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RELATED PCT APPLICATION NUMBER: PCT/US03/18923

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Date of Deposit: 6/17/2002

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: C. Frank Bennett, Susan M. Freier and Kenneth W. Dobie

For: Antisense Modulation of SMRT Expression

BOX SEQUENCE

Assistant Commissioner for Patents  
Washington DC 20231

10978 U.S. PTO  
10/17/02

PATENT APPLICATION TRANSMITTAL LETTER

Transmitted herewith for filing, please find the following:

- The specification of the above-referenced patent application;
- An executed Declaration or Oath and Power of Attorney;
- ✓ An Assignment of the invention to Isis Pharmaceuticals Inc. with recordation cover sheet (PTO Form PTO-1595) and \$40.00 cover fee;
- Statement to Support Filing and Submission of DNA/Amino Acid Sequences in Accordance with 37 CFR § 1.821 through 1.825;
- Sequence listing in computer readable form in accordance with 37 C.F.R. § 1.821(e); and
- An Information Disclosure Statement with references.

The filing fee has been calculated as shown below:


For:	No. Filed	No. Extra	Rate	Fee
BASE FEE				\$740.00
Total Claims	20 - 20 =	0	X \$9=	\$0
Indep. Claims	2 - 3 =	0	x\$40=	\$0
TOTAL				\$ 740.00

The Commissioner is hereby authorized to charge the following fees to Deposit Account No. 500252:

- the amount of \$780.00 for the above listed fees;
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- any additional filing fees required under 37 CFR 1.16 including fees for presentation of extra claims; and
- any additional patent application processing fees under 37 CFR 1.17 and under 37 CFR 1.20 (d).

Triplicate copies of this transmittal are enclosed.

Date: June 17, 2002

  
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Inventor(s): C. Frank Bennett, Susan M. Freier and Kenneth W. Dobie

Serial No.: not yet assigned

Filing Date: herewith

Title: **Antisense Modulation of SMRT Expression**

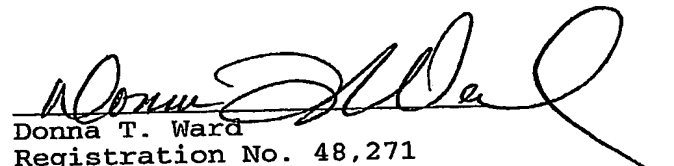
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**STATEMENT TO SUPPORT FILING AND SUBMISSION IN ACCORDANCE WITH 37  
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I hereby state, in accordance with the requirements of 37  
C.F.R. §1.821(f), that the contents of the paper and computer  
readable copies of the Sequence Listing, submitted in accordance with  
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**ANTISENSE MODULATION OF SMRT EXPRESSION****FIELD OF THE INVENTION**

10       The present invention provides compositions and methods  
for modulating the expression of SMRT. In particular, this  
invention relates to compounds, particularly  
oligonucleotides, specifically hybridizable with nucleic  
acids encoding SMRT. Such compounds have been shown to  
15       modulate the expression of SMRT.

**BACKGROUND OF THE INVENTION**

      Steroids, retinoids, thyroid hormones, and vitamin D  
play critical roles in the regulation of reproduction,  
20       development, metabolism, and homeostasis. The intracellular  
receptors for these hormones and lipophilic compounds  
comprise a large family of transcription factors that  
regulate ligand-dependent expression of target genes. This  
family can be divided into two classes: the steroid receptors  
25       are normally inactive and associated with heat shock proteins  
in the absence of hormone, and the nuclear hormone receptors,  
which bind DNA and repress transcription in the absence of  
ligand and activate transcription upon ligand treatment. By  
activating or repressing target genes, the steroid/nuclear  
30       hormone receptors elicit a broad range of cellular responses,  
such as differentiation, proliferation, and cell death (Chen  
and Li, *Crit. Rev. Eukaryot. Gene Expr.*, 1998, 8, 169-190).

      The highly ordered chromatin structure of chromosomal  
DNA within the nuclei of eukaryotic cells presents a physical  
35       obstacle for gene transcription, by limiting access of



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transcription factors and RNA polymerase II core machinery to DNA templates. Posttranslational modifications such as phosphorylation, acetylation, ADP-ribosylation, and ubiquitination can reversibly modify histone proteins within chromatin, and these histone modifications affect structural alterations in local chromatin architecture during transcription. The dynamic state of histone acetylation is tightly regulated and maintained by histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzyme activities.

10 Histone modification plays a pivotal role in controlling access of transcriptional activators, repressors, and the basal transcription machinery to regulatory sequences in the underlying DNA template to positively or negatively affect the rate of gene transcription. Hyperacetylation of core

15 histones in gene promoters results in decondensation of chromatin, increases accessibility of transcription factors, and is correlated with gene activation. Conversely, hypoacetylation is thought to reestablish the condensed chromatin structure, favoring transcriptional repression and gene silencing (Chen and Li, *Crit. Rev. Eukaryot. Gene Expr.*, 1998, 8, 169-190; Xu et al., *Curr. Opin. Genet. Dev.*, 1999, 9, 140-147).

Repression of basal transcription by nuclear hormone receptors such as thyroid receptor (TR) and retinoic acid

25 receptor (RAR) plays a critical role in oncogenesis and cellular differentiation. Several cofactors of nuclear receptors have been identified as important components of transcriptional regulation, and these coactivators and corepressors have been found to harbor intrinsic HAT and HDAC

30 activities, respectively. The nuclear receptor corepressors, N-CoR and SMRT, interact with several unliganded nuclear receptors and recruit multisubunit protein complexes containing HDACs and several other proteins. Furthermore, recent studies of RAR and TR nuclear hormone receptors have

35 revealed that, upon ligand binding, a HDAC-containing complex is displaced from the nuclear receptor in exchange for binding of a HAT-containing complex to promoters of target

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genes. Thus, ligand-dependent recruitment of chromatin-remodeling activities, in the form of histone acetylation and deacetylation enzyme complexes, is believed to serve as a general mechanism underlying the switch of nuclear receptors from a transcriptionally repressed to a transcriptionally active state (Xu et al., *Curr. Opin. Genet. Dev.*, 1999, 9, 140-147).

Nuclear hormone corepressor proteins have been demonstrated to associate with mSin3 and HDAC-containing complexes, presumably to induce chromatin condensation and in doing so, these corepressors modulate transcriptional activation or silencing of a wide variety of gene targets involved in development, differentiation, and cellular proliferation (Lee et al., *J. Biol. Chem.*, 2000, 275, 12470-12474; Li et al., *Embo J.*, 2000, 19, 4342-4350; Wu et al., *J. Biol. Chem.*, 2001, 276, 24177-24185).

SMRT (also known as silencing mediator for retinoid and thyroid hormone action, Nuclear receptor co-repressor 2, NCoR2, TRAC-1, CTG26, TNRC14, and SMRTe) was originally identified and cloned from a human B-cell cDNA library as a RAR-interacting protein in a two-hybrid screen (Chen and Evans, *Nature*, 1995, 377, 454-457). RAR and TR directly interact with SMRT, and these protein-protein interactions bring the receptors to target promoters in the nucleus, resulting in gene repression. Ligand binding to the receptors causes dissociation of SMRT from them, resulting in ligand-dependent activation of target genes (Chen and Evans, *Nature*, 1995, 377, 454-457). In an accompanying paper, nuclear receptor corepressor (N-CoR) was identified and found to be related to SMRT; thus, the name TRAC was proposed for a newly identified family of thyroid-hormone- and retinoic-acid-receptor-associated corepressor proteins (Horlein et al., *Nature*, 1995, 377, 397-404).

The original isolate of SMRT showed significant homology to N-CoR, but was substantially shorter in length. A longer isoform was later isolated and named SMRT, as it was predicted to be the major form *in vivo*, and the shorter,

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original isolate was renamed s-SMRT (Ordentlich et al., *Proc. Natl. Acad. Sci. U. S. A.*, 1999, 96, 2639-2644).

Concurrently, a second group independently identified the human and mouse SMRT-extended (SMRTe) isoforms, which  
5 included 1000 amino acids at the N-terminus bearing striking similarity to N-CoR, and found that SMRTe expression was cell-cycle regulated and transcripts were present in many mouse embryonic tissues (Park et al., *Proc. Natl. Acad. Sci. U. S. A.*, 1999, 96, 3519-3524). Furthermore, a polyclonal  
10 antibody has been generated against SMRT and used to study its cell cycle dependent localization. SMRT is ubiquitously expressed in the nuclei of all interphase cells, and is found to be dispersed in the cytoplasm and excluded from the metaphase chromosomes in mitotic cells (Chen et al., *Proc. Natl. Acad. Sci. U. S. A.*, 1996, 93, 7567-7571). The relative  
15 levels of SMRT expression also vary with tissue type and upon hormone treatment (Misiti et al., *Endocrinology*, 1998, 139, 2493-2500).

Posttranslational modification of SMRT may alter its  
20 subcellular localization and its ability to interact with nuclear hormone receptors. SMRT is a substrate for phosphorylation by multiple components of the mitogen-activated protein kinase (MAPK) cascade that operates downstream of the epidermal growth factor (EGF) receptor, and  
25 this phosphorylation appears to inhibit the ability of SMRT to bind to nuclear receptors, and correlates with a relocalization from the nucleus to the cytoplasm (Hong and Privalsky, *Mol. Cell. Biol.*, 2000, 20, 6612-6625).

Nuclear receptors inhibit synthesis of matrix  
30 metalloproteinase-1 (MMP-1), an enzyme that degrades interstitial collagens and contributes to the pathology in numerous disorders, including the joint erosion observed in rheumatoid arthritis. Primary synovial fibroblasts express SMRT, and overexpression of SMRT was found to inhibit MMP-1  
35 promoter activity, suggesting that SMRT maintains a repressive state of the MMP-1 gene and strictly controls

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regulation of interstitial collagenase (Schroen et al.,  
*Biochem. Biophys. Res. Commun.*, 1997, 237, 52-58).

In addition to its role in inflammation, SMRT plays a  
role in several cancers. The MCF-7 breast cancer cell line  
5 expresses the aryl hydrocarbon receptor (AhR) and AhR nuclear  
translocator (Arnt), and SMRT physically as well as  
functionally interacts with these proteins, suggesting that  
nuclear receptor corepressors can modulate aryl hydrocarbon  
responsiveness in breast cancer cells (Nguyen et al., *Arch.*  
10 *Biochem. Biophys.*, 1999, 367, 250-257).

Mutations in members of the nuclear receptor superfamily  
frequently result in neoplastic and endocrine disorders. The  
genetic disease characterized by resistance to thyroid  
hormone (RTH) exemplifies such a disorder. RTH is attributed  
15 to mutations in the TR $\beta$  allele of the thyroid hormone  
receptor. These mutations act in a dominant negative manner,  
interfering with receptor function and displaying an aberrant  
association with SMRT, in which ligand treatment no longer  
results in dissociation of SMRT from the receptor (Matsushita  
20 et al., *J. Endocrinol.*, 2000, 167, 493-503).

SMRT is also involved in human acute promyelocytic  
leukemia (APL), in which the majority of patients harbor a  
specific gene translocation involving the RAR $\alpha$  allele. At  
least five different fusion partners of RAR $\alpha$  have been  
25 identified, but the two best-studied fusion proteins, PML-  
RAR $\alpha$  and PLZF-RAR $\alpha$  retain a wild-type affinity for retinoic  
acid (RA), and are able to bind to promoters of retinoic acid  
responsive genes. The PML-RAR $\alpha$  and PLZF-RAR $\alpha$  fusions have  
increased affinity for the corepressor SMRT, and the  
30 dissociation of SMRT from RAR normally induced by RA no  
longer occurs, leading to aberrant expression of target  
genes. Thus, PML-RAR $\alpha$  and PLZF-RAR $\alpha$  are leukemogenic at  
physiological concentrations of RA (Lin and Evans, *Mol.*  
*Cell.*, 2000, 5, 821-830).

35 The pharmacological modulation of the activity and/or  
expression components of SMRT corepressor-containing

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complexes is believed to be an appropriate point of therapeutic intervention in pathological conditions such as inflammatory or autoimmune diseases, rheumatoid arthritis, resistance to thyroid hormone and other metabolic diseases, and cancers such as acute promyelocytic leukemia.

Disclosed and claimed in WO 00/53734 are nucleic acids encoding SMRT, allelic variants of SMRT, nucleic acids with 90% homology to SMRT or which can hybridize to SMRT, as well as BAC, PAC, and cosmid clones comprising genomic or cDNA sequences encoding SMRT, DNA constructs and expression cassettes bearing suitable regulatory sequences for expression of SMRT as a biologically active protein, antisense targeted to the SMRT gene, and antibodies against the SMRT protein. Further claimed are host cells containing said nucleic acid molecules and methods for producing polypeptides encoded by SMRT, or fragments thereof, as well as the use of the DNA or polypeptide sequences of SMRT as tools to identify potential drugs for the treatment of angiogenic diseases, rheumatoid arthritis, psoriasis, eye diseases such as diabetic retinopathy and neovascular glaucoma, kidney diseases such as glomerulonephritis and diabetic nephropathy (Thierauch et al., 2000).

Currently, there are no known therapeutic agents which effectively inhibit the synthesis of SMRT and investigative strategies aimed at studying SMRT function have involved the use of antibodies for cellular localization studies (Chen et al., *Proc. Natl. Acad. Sci. U. S. A.*, 1996, 93, 7567-7571).

Consequently, there exists a long felt need to identify methods of modulating transcriptional repression complexes and specifically for agents capable of effectively modulating SMRT function.

Antisense technology is emerging as an effective means for reducing the expression of specific gene products and may therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications for the modulation of SMRT expression.

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The present invention provides compositions and methods for modulating SMRT expression, including modulation of the extended isoform of SMRT, known as SMRTe.

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# **SUMMARY OF THE INVENTION**

The present invention is directed to compounds, particularly antisense oligonucleotides, which are targeted to a nucleic acid encoding SMRT, and which modulate the expression of SMRT. Pharmaceutical and other compositions comprising the compounds of the invention are also provided. Further provided are methods of modulating the expression of SMRT in cells or tissues comprising contacting said cells or tissues with one or more of the antisense compounds or compositions of the invention. Further provided are methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of SMRT by administering a therapeutically or prophylactically effective amount of one or more of the antisense compounds or compositions of the invention.

## **DETAILED DESCRIPTION OF THE INVENTION**

The present invention employs oligomeric compounds, particularly antisense oligonucleotides, for use in modulating the function of nucleic acid molecules encoding SMRT, ultimately modulating the amount of SMRT produced. This is accomplished by providing antisense compounds which specifically hybridize with one or more nucleic acids encoding SMRT. As used herein, the terms "target nucleic acid" and "nucleic acid encoding SMRT" encompass DNA encoding SMRT, RNA (including pre-mRNA and mRNA) transcribed from such DNA, and also cDNA derived from such RNA. The specific hybridization of an oligomeric compound with its target nucleic acid interferes with the normal function of the nucleic acid. This modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "antisense". The functions of

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DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with include all vital functions such as, for example, translocation of the RNA to the site of protein translation, translocation of the RNA to sites within the cell which are distant from the site of RNA synthesis, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA. The overall effect of such interference with target nucleic acid function is modulation of the expression of SMRT. In the context of the present invention, "modulation" means either an increase (stimulation) or a decrease (inhibition) in the expression of a gene. In the context of the present invention, inhibition is the preferred form of modulation of gene expression and mRNA is a preferred target.

It is preferred to target specific nucleic acids for antisense. "Targeting" an antisense compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins with the identification of a nucleic acid sequence whose function is to be modulated. This may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. In the present invention, the target is a nucleic acid molecule encoding SMRT. The targeting process also includes determination of a site or sites within this gene for the antisense interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within the context of the present invention, a preferred intragenic site is the region encompassing the translation initiation or termination codon of the open reading frame (ORF) of the gene. Since, as is known in the art, the translation initiation codon is typically 5'-AUG (in transcribed mRNA molecules; 5'-ATG in the corresponding DNA molecule), the translation initiation codon is also referred

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to as the "AUG codon," the "start codon" or the "AUG start  
codon". A minority of genes have a translation initiation  
codon having the RNA sequence 5'-GUG, 5'-UUG or 5'-CUG, and  
5'-AUA, 5'-ACG and 5'-CUG have been shown to function in  
5 vivo. Thus, the terms "translation initiation codon" and  
"start codon" can encompass many codon sequences, even though  
the initiator amino acid in each instance is typically  
methionine (in eukaryotes) or formylmethionine (in  
10 prokaryotes). It is also known in the art that eukaryotic  
and prokaryotic genes may have two or more alternative start  
codons, any one of which may be preferentially utilized for  
translation initiation in a particular cell type or tissue,  
or under a particular set of conditions. In the context of  
the invention, "start codon" and "translation initiation  
15 codon" refer to the codon or codons that are used in vivo to  
initiate translation of an mRNA molecule transcribed from a  
gene encoding SMRT, regardless of the sequence(s) of such  
codons.

It is also known in the art that a translation  
20 termination codon (or "stop codon") of a gene may have one of  
three sequences, i.e., 5'-UAA, 5'-UAG and 5'-UGA (the  
corresponding DNA sequences are 5'-TAA, 5'-TAG and 5'-TGA,  
respectively). The terms "start codon region" and  
"translation initiation codon region" refer to a portion of  
25 such an mRNA or gene that encompasses from about 25 to about  
50 contiguous nucleotides in either direction (i.e., 5' or  
3') from a translation initiation codon. Similarly, the  
terms "stop codon region" and "translation termination codon  
region" refer to a portion of such an mRNA or gene that  
30 encompasses from about 25 to about 50 contiguous nucleotides  
in either direction (i.e., 5' or 3') from a translation  
termination codon.

The open reading frame (ORF) or "coding region," which  
is known in the art to refer to the region between the  
35 translation initiation codon and the translation termination  
codon, is also a region which may be targeted effectively.  
Other target regions include the 5' untranslated region



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(5'UTR), known in the art to refer to the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene, and the 3' untranslated region (3'UTR), known in the art to refer to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene. The 5' cap of an mRNA comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage. The 5' cap region of an mRNA is considered to include the 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap. The 5' cap region may also be a preferred target region.

Although some eukaryotic mRNA transcripts are directly translated, many contain one or more regions, known as "introns," which are excised from a transcript before it is translated. The remaining (and therefore translated) regions are known as "exons" and are spliced together to form a continuous mRNA sequence. mRNA splice sites, i.e., intron-exon junctions, may also be preferred target regions, and are particularly useful in situations where aberrant splicing is implicated in disease, or where an overproduction of a particular mRNA splice product is implicated in disease. Aberrant fusion junctions due to rearrangements or deletions are also preferred targets. mRNA transcripts produced via the process of splicing of two (or more) mRNAs from different gene sources are known as "fusion transcripts". It has also been found that introns can be effective, and therefore preferred, target regions for antisense compounds targeted, for example, to DNA or pre-mRNA.

It is also known in the art that alternative RNA transcripts can be produced from the same genomic region of DNA. These alternative transcripts are generally known as "variants". More specifically, "pre-mRNA variants" are

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transcripts produced from the same genomic DNA that differ from other transcripts produced from the same genomic DNA in either their start or stop position and contain both intronic and extronic regions.

5        Upon excision of one or more exon or intron regions or portions thereof during splicing, pre-mRNA variants produce smaller "mRNA variants". Consequently, mRNA variants are processed pre-mRNA variants and each unique pre-mRNA variant must always produce a unique mRNA variant as a result of  
10        splicing. These mRNA variants are also known as "alternative splice variants". If no splicing of the pre-mRNA variant occurs then the pre-mRNA variant is identical to the mRNA variant.

         It is also known in the art that variants can be  
15        produced through the use of alternative signals to start or stop transcription and that pre-mRNAs and mRNAs can possess more than one start codon or stop codon. Variants that originate from a pre-mRNA or mRNA that use alternative start codons are known as "alternative start variants" of that pre-mRNA or mRNA. Those transcripts that use an alternative stop  
20        codon are known as "alternative stop variants" of that pre-mRNA or mRNA. One specific type of alternative stop variant is the "polyA variant" in which the multiple transcripts produced result from the alternative selection of one of the  
25        "polyA stop signals" by the transcription machinery, thereby producing transcripts that terminate at unique polyA sites.

         Once one or more target sites have been identified, oligonucleotides are chosen which are sufficiently complementary to the target, i.e., hybridize sufficiently  
30        well and with sufficient specificity, to give the desired effect.

         In the context of this invention, "hybridization" means hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary  
35        nucleoside or nucleotide bases. For example, adenine and thymine are complementary nucleobases which pair through the formation of hydrogen bonds. "Complementary," as used

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herein, refers to the capacity for precise pairing between two nucleotides. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at the same position of a DNA or RNA molecule, then the oligonucleotide and the DNA or RNA are considered to be complementary to each other at that position. The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable.

An antisense compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of activity, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed. It is preferred that the antisense compounds of the present invention comprise at least 80% sequence complementarity to a target region within the target nucleic acid, moreover that they comprise 90% sequence complementarity and even more comprise 95% sequence complementarity to the target region within the target nucleic acid sequence to which they are targeted. For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary, and would therefore specifically hybridize, to a target

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region would represent 90 percent complementarity. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using basic local alignment search tools (BLAST programs) (Altschul et al., *J. Mol. Biol.*, **1990**, 215, 403-410; Zhang and Madden, *Genome Res.*, **1997**, 7, 649-656).

Antisense and other compounds of the invention, which hybridize to the target and inhibit expression of the target, are identified through experimentation, and representative sequences of these compounds are hereinbelow identified as preferred embodiments of the invention. The sites to which these preferred antisense compounds are specifically hybridizable are hereinbelow referred to as "preferred target regions" and are therefore preferred sites for targeting. As used herein the term "preferred target region" is defined as at least an 8-nucleobase portion of a target region to which an active antisense compound is targeted. While not wishing to be bound by theory, it is presently believed that these target regions represent regions of the target nucleic acid which are accessible for hybridization.

While the specific sequences of particular preferred target regions are set forth below, one of skill in the art will recognize that these serve to illustrate and describe particular embodiments within the scope of the present invention. Additional preferred target regions may be identified by one having ordinary skill.

Target regions 8-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative preferred target regions are considered to be suitable preferred target regions as well.

Exemplary good preferred target regions include DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 5'-terminus of one of the illustrative preferred target regions (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5'-terminus of the target region

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and continuing until the DNA or RNA contains about 8 to about 80 nucleobases). Similarly good preferred target regions are represented by DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative preferred target regions (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3'-terminus of the target region and continuing until the DNA or RNA contains about 8 to about 80 nucleobases). One having skill in the art, once armed with the empirically-derived preferred target regions illustrated herein will be able, without undue experimentation, to identify further preferred target regions. In addition, one having ordinary skill in the art will also be able to identify additional compounds, including oligonucleotide probes and primers, that specifically hybridize to these preferred target regions using techniques available to the ordinary practitioner in the art.

Antisense compounds are commonly used as research reagents and diagnostics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. Antisense compounds are also used, for example, to distinguish between functions of various members of a biological pathway. Antisense modulation has, therefore, been harnessed for research use.

For use in kits and diagnostics, the antisense compounds of the present invention, either alone or in combination with other antisense compounds or therapeutics, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of a portion or the entire complement of genes expressed within cells and tissues.

Expression patterns within cells or tissues treated with one or more antisense compounds are compared to control cells or tissues not treated with antisense compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease

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association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

Examples of methods of gene expression analysis known in the art include DNA arrays or microarrays (Brazma and Vilo, *FEBS Lett.*, **2000**, 480, 17-24; Celis, et al., *FEBS Lett.*, **2000**, 480, 2-16), SAGE (serial analysis of gene expression) (Madden, et al., *Drug Discov. Today*, **2000**, 5, 415-425), READS (restriction enzyme amplification of digested cDNAs) (Prashar and Weissman, *Methods Enzymol.*, **1999**, 303, 258-72), TOGA (total gene expression analysis) (Sutcliffe, et al., *Proc. Natl. Acad. Sci. U. S. A.*, **2000**, 97, 1976-81), protein arrays and proteomics (Celis, et al., *FEBS Lett.*, **2000**, 480, 2-16; Jungblut, et al., *Electrophoresis*, **1999**, 20, 2100-10), expressed sequence tag (EST) sequencing (Celis, et al., *FEBS Lett.*, **2000**, 480, 2-16; Larsson, et al., *J. Biotechnol.*, **2000**, 80, 143-57), subtractive RNA fingerprinting (SuRF) (Fuchs, et al., *Anal. Biochem.*, **2000**, 286, 91-98; Larson, et al., *Cytometry*, **2000**, 41, 203-208), subtractive cloning, differential display (DD) (Jurecic and Belmont, *Curr. Opin. Microbiol.*, **2000**, 3, 316-21), comparative genomic hybridization (Carulli, et al., *J. Cell Biochem. Suppl.*, **1998**, 31, 286-96), FISH (fluorescent in situ hybridization) techniques (Going and Gusterson, *Eur. J. Cancer*, **1999**, 35, 1895-904) and mass spectrometry methods (reviewed in To, *Comb. Chem. High Throughput Screen*, **2000**, 3, 235-41).

The specificity and sensitivity of antisense is also harnessed by those of skill in the art for therapeutic uses. Antisense oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that oligonucleotides can be useful therapeutic

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modalities that can be configured to be useful in treatment regimes for treatment of cells, tissues and animals, especially humans.

In the context of this invention, the term  
 5 "oligonucleotide" refers to an oligomer or polymer of  
 ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or  
 mimetics thereof. This term includes oligonucleotides  
 composed of naturally-occurring nucleobases, sugars and  
 covalent internucleoside (backbone) linkages as well as  
 10 oligonucleotides having non-naturally-occurring portions  
 which function similarly. Such modified or substituted  
 oligonucleotides are often preferred over native forms  
 because of desirable properties such as, for example,  
 enhanced cellular uptake, enhanced affinity for nucleic acid  
 15 target and increased stability in the presence of nucleases.

While antisense oligonucleotides are a preferred  
 form of antisense compound, the present invention comprehends  
 other oligomeric antisense compounds, including but not  
 limited to oligonucleotide mimetics such as are described  
 20 below. The antisense compounds in accordance with this  
 invention preferably comprise from about 8 to about 80  
 nucleobases (i.e. from about 8 to about 80 linked  
 nucleosides). Particularly preferred antisense compounds are  
 antisense oligonucleotides from about 8 to about 50  
 25 nucleobases, even more preferably those comprising from about  
 12 to about 30 nucleobases. Antisense compounds include  
 ribozymes, external guide sequence (EGS) oligonucleotides  
 (oligozymes), and other short catalytic RNAs or catalytic  
 oligonucleotides which hybridize to the target nucleic acid  
 30 and modulate its expression.

Antisense compounds 8-80 nucleobases in length  
 comprising a stretch of at least eight (8) consecutive  
 nucleobases selected from within the illustrative antisense  
 compounds are considered to be suitable antisense compounds  
 35 as well.

Exemplary preferred antisense compounds include DNA or  
 RNA sequences that comprise at least the 8 consecutive

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nucleobases from the 5'-terminus of one of the illustrative preferred antisense compounds (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5'-terminus of the antisense  
5 compound which is specifically hybridizable to the target nucleic acid and continuing until the DNA or RNA contains about 8 to about 80 nucleobases). Similarly preferred antisense compounds are represented by DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the  
10 3'-terminus of one of the illustrative preferred antisense compounds (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3'-terminus of the antisense compound which is specifically hybridizable to the target nucleic acid and  
15 continuing until the DNA or RNA contains about 8 to about 80 nucleobases). One having skill in the art, once armed with the empirically-derived preferred antisense compounds illustrated herein will be able, without undue experimentation, to identify further preferred antisense  
20 compounds.

Antisense and other compounds of the invention, which hybridize to the target and inhibit expression of the target, are identified through experimentation, and representative sequences of these compounds are herein identified as  
25 preferred embodiments of the invention. While specific sequences of the antisense compounds are set forth herein, one of skill in the art will recognize that these serve to illustrate and describe particular embodiments within the scope of the present invention. Additional preferred  
30 antisense compounds may be identified by one having ordinary skill.

As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic base. The two most common classes of such  
35 heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the



Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotri-  
30 esters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates,  
35 thionoalkylphosphotriesters, selenophosphates and borano-phosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or

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more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside  
5 residue which may be abasic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included.

Representative United States patents that teach the preparation of the above phosphorus-containing linkages  
10 include, but are not limited to, U.S.: 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253;  
15 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, certain of which are commonly owned with this application, and each of which is herein incorporated by reference.

Preferred modified oligonucleotide backbones that do not  
20 include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These  
25 include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene  
30 containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH<sub>2</sub> component parts.

Representative United States patents that teach the  
35 preparation of the above oligonucleosides include, but are not limited to, U.S.: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564;

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5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677;  
5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289;  
5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070;  
5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and  
5 5,677,439, certain of which are commonly owned with this  
application, and each of which is herein incorporated by  
reference.

In other preferred oligonucleotide mimetics, both the  
sugar and the internucleoside linkage, i.e., the backbone, of  
10 the nucleotide units are replaced with novel groups. The  
base units are maintained for hybridization with an  
appropriate nucleic acid target compound. One such  
oligomeric compound, an oligonucleotide mimetic that has been  
shown to have excellent hybridization properties, is referred  
15 to as a peptide nucleic acid (PNA). In PNA compounds, the  
sugar-backbone of an oligonucleotide is replaced with an  
amide containing backbone, in particular an aminoethylglycine  
backbone. The nucleobases are retained and are bound  
directly or indirectly to aza nitrogen atoms of the amide  
20 portion of the backbone. Representative United States  
patents that teach the preparation of PNA compounds include,  
but are not limited to, U.S.: 5,539,082; 5,714,331; and  
5,719,262, each of which is herein incorporated by reference.  
Further teaching of PNA compounds can be found in Nielsen et  
25 al., *Science*, **1991**, 254, 1497-1500.

Most preferred embodiments of the invention are  
oligonucleotides with phosphorothioate backbones and  
oligonucleosides with heteroatom backbones, and in particular  
-CH<sub>2</sub>-NH-O-CH<sub>2</sub>-, -CH<sub>2</sub>-N(CH<sub>3</sub>)-O-CH<sub>2</sub>- [known as a methylene  
30 (methylimino) or MMI backbone], -CH<sub>2</sub>-O-N(CH<sub>3</sub>)-CH<sub>2</sub>-, -CH<sub>2</sub>-N(CH<sub>3</sub>)-  
N(CH<sub>3</sub>)-CH<sub>2</sub>- and -O-N(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>- [wherein the native  
phosphodiester backbone is represented as -O-P-O-CH<sub>2</sub>-] of the  
above referenced U.S. patent 5,489,677, and the amide  
backbones of the above referenced U.S. patent 5,602,240.  
35 Also preferred are oligonucleotides having morpholino  
backbone structures of the above-referenced U.S. patent  
5,034,506.

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Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or  
5 O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C<sub>1</sub> to C<sub>10</sub> alkyl or C<sub>2</sub> to C<sub>10</sub> alkenyl and alkynyl. Particularly preferred are

O[(CH<sub>2</sub>)<sub>n</sub>O]<sub>m</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>OCH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, O(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>ONH<sub>2</sub>, and  
O(CH<sub>2</sub>)<sub>n</sub>ON[(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>]<sub>2</sub>, where n and m are from 1 to about 10.

10 Other preferred oligonucleotides comprise one of the following at the 2' position: C<sub>1</sub> to C<sub>10</sub> lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH<sub>3</sub>, OCN, Cl, Br, CN, CF<sub>3</sub>, OCF<sub>3</sub>, SOCH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>, ONO<sub>2</sub>, NO<sub>2</sub>, N<sub>3</sub>, NH<sub>2</sub>, heterocycloalkyl,  
15 heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and  
20 other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-  
25 dimethylaminoethoxy, i.e., a O(CH<sub>2</sub>)<sub>2</sub>ON(CH<sub>3</sub>)<sub>2</sub> group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethyl-amino-ethoxy-ethyl or 2'-DMAEOE), i.e., 2'-O-CH<sub>2</sub>-O-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, also described in examples hereinbelow.

30 Other preferred modifications include 2'-methoxy (2'-O-CH<sub>3</sub>), 2'-aminopropoxy (2'-OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>), 2'-allyl (2'-CH<sub>2</sub>-CH=CH<sub>2</sub>), 2'-O-allyl (2'-O-CH<sub>2</sub>-CH=CH<sub>2</sub>) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is  
35 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-

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5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

A further preferred modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene (-CH<sub>2</sub>-) group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH<sub>3</sub>) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-

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methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine  
 5 cytidine(1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-  
 10 pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine  
 15 and 2-pyridone. Further nucleobases include those disclosed in United States Patent No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J.I., ed. John Wiley & Sons, 1990, those disclosed by Englisch et al., *Angewandte Chemie*,  
 20 International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, pages 289-302, Crooke, S.T. and Lebleu, B. , ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of  
 25 the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex  
 30 stability by 0.6-1.2°C (Sanghvi, Y.S., Crooke, S.T. and Lebleu, B., eds., *Antisense Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

35 Representative United States patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include,

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but are not limited to, the above noted U.S. 3,687,808, as well as U.S.: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5 5,596,091; 5,614,617; 5,645,985; 5,830,653; 5,763,588; 6,005,096; and 5,681,941, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference, and United States patent 10 application and also herein incorporated by reference.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the 15 oligonucleotide. The compounds of the invention can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, 20 groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterols, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluores- 25 ceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve oligomer uptake, enhance oligomer resistance to degradation, and/or strengthen sequence-specific hybridization with RNA. Groups that 30 enhance the pharmacokinetic properties, in the context of this invention, include groups that improve oligomer uptake, distribution, metabolism or excretion. Representative conjugate groups are disclosed in International Patent Application PCT/US92/09196, filed October 23, 1992 the entire 35 disclosure of which is incorporated herein by reference. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al.,

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Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxcholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937). Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in United States Patent Application 09/334,130 (filed June 15, 1999) which is incorporated herein by reference in its entirety.

Representative United States patents that teach the preparation of such oligonucleotide conjugates include, but are not limited to, U.S.: 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802;



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5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718;  
5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779;  
4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582;  
4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830;  
5 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506;  
5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241,  
5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667;  
5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481;  
5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and  
10 5,688,941, certain of which are commonly owned with the  
instant application, and each of which is herein incorporated  
by reference.

It is not necessary for all positions in a given  
compound to be uniformly modified, and in fact more than one  
15 of the aforementioned modifications may be incorporated in a  
single compound or even at a single nucleoside within an  
oligonucleotide. The present invention also includes  
antisense compounds which are chimeric compounds. "Chimeric"  
antisense compounds or "chimeras," in the context of this  
20 invention, are antisense compounds, particularly  
oligonucleotides, which contain two or more chemically  
distinct regions, each made up of at least one monomer unit,  
i.e., a nucleotide in the case of an oligonucleotide  
compound. These oligonucleotides typically contain at least  
25 one region wherein the oligonucleotide is modified so as to  
confer upon the oligonucleotide increased resistance to  
nuclease degradation, increased cellular uptake, increased  
stability and/or increased binding affinity for the target  
nucleic acid. An additional region of the oligonucleotide  
30 may serve as a substrate for enzymes capable of cleaving  
RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a  
cellular endonuclease which cleaves the RNA strand of an  
RNA:DNA duplex. Activation of RNase H, therefore, results in  
cleavage of the RNA target, thereby greatly enhancing the  
35 efficiency of oligonucleotide inhibition of gene expression.  
The cleavage of RNA:RNA hybrids can, in like fashion, be  
accomplished through the actions of endoribonucleases, such

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as interferon-induced RNaseL which cleaves both cellular and viral RNA. Consequently, comparable results can often be obtained with shorter oligonucleotides when chimeric oligonucleotides are used, compared to phosphorothioate deoxyoligonucleotides hybridizing to the same target region. 5 Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

Chimeric antisense compounds of the invention may be 10 formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the 15 preparation of such hybrid structures include, but are not limited to, U.S.: 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, certain of which are commonly owned with the instant application, and each of 20 which is herein incorporated by reference in its entirety.

The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for 25 example, Applied Biosystems (Foster City, CA). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives.

30 The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor-targeted molecules, oral, rectal, topical or other formulations, for assisting in 35 uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption-assisting formulations

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include, but are not limited to, U.S.: 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

The antisense compounds of the invention encompass any 10 pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure 15 is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents.

The term "prodrug" indicates a therapeutic agent that is prepared in an inactive form that is converted to an active 20 form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions. In particular, prodrug versions of the oligonucleotides of the invention are prepared as SATE [(S-acetyl-2-thioethyl) phosphate] derivatives according to 25 the methods disclosed in WO 93/24510 to Gosselin et al., published December 9, 1993 or in WO 94/26764 and U.S. 5,770,713 to Imbach et al.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the 30 compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline 35 earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are

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N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge et al., "Pharmaceutical Salts," *J. of Pharma Sci.*, 1977, 66, 1-19). The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention. As used herein, a "pharmaceutical addition salt" includes a pharmaceutically acceptable salt of an acid form of one of the components of the compositions of the invention. These include organic or inorganic acid salts of the amines. Preferred acid salts are the hydrochlorides, acetates, salicylates, nitrates and phosphates. Other suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of a variety of inorganic and organic acids, such as, for example, with inorganic acids, such as for example hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, lactic acid, oxalic acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid; and with amino acids, such as the 20 alpha-amino acids involved in the synthesis of proteins in nature, for example glutamic acid or aspartic acid, and also with phenylacetic acid, methanesulfonic acid, ethanesulfonic

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acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate,

5 N-cyclohexylsulfamic acid (with the formation of cyclamates), or with other acid organic compounds, such as ascorbic acid. Pharmaceutically acceptable salts of compounds may also be prepared with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those

10 skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations. Carbonates or hydrogen carbonates are also possible.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited

15 to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the

20 like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid,

25 naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine.

The antisense compounds of the present invention can be

30 utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. For therapeutics, an animal, preferably a human, suspected of having a disease or disorder which can be treated by modulating the expression of SMRT is treated by administering antisense compounds in accordance

35 with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an antisense compound to a suitable

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pharmaceutically acceptable diluent or carrier. Use of the antisense compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation or tumor formation, for example.

5 The antisense compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding SMRT, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the antisense oligonucleotides of the  
10 invention with a nucleic acid encoding SMRT can be detected by means known in the art. Such means may include conjugation of an enzyme to the oligonucleotide, radiolabelling of the oligonucleotide or any other suitable detection means. Kits using such detection means for  
15 detecting the level of SMRT in a sample may also be prepared.

The present invention also includes pharmaceutical compositions and formulations which include the antisense compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of  
20 ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including  
25 by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular,  
30 administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments,  
35 lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be

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necessary or desirable. Coated condoms, gloves and the like may also be useful. Preferred topical formulations include those in which the oligonucleotides of the invention are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Preferred lipids and liposomes include neutral (e.g. dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline) negative (e.g. dimyristoylphosphatidyl glycerol DMPG) and cationic (e.g. dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). Oligonucleotides of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, oligonucleotides may be complexed to lipids, in particular to cationic lipids. Preferred fatty acids and esters include but are not limited arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C<sub>1-10</sub> alkyl ester (e.g. isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in United States patent application 09/315,298 filed on May 20, 1999 which is incorporated herein by reference in its entirety.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitables. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. Preferred oral formulations are those in which oligonucleotides of the invention are administered in conjunction with one or more penetration enhancers surfactants and chelators. Preferred surfactants include

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fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Preferred bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Preferred fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (e.g. sodium). Also preferred are combinations of penetration enhancers, for example, fatty acids/salts in combination with bile acids/salts. A particularly preferred combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. Oligonucleotides of the invention may be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. Oligonucleotide complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Particularly preferred complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylamino-methylethylene P(TDAE), polyaminostyrene (e.g. p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcyanoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-



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dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for oligonucleotides and their preparation are described in detail in United States applications 08/886,829 (filed July 1, 1997), 09/108,673 (filed July 1, 1998), 09/256,515 (filed February 23, 1999), 09/082,624 (filed May 21, 1998) and 09/315,298 (filed May 20, 1999), each of which is incorporated herein by reference in their entirety.

10 Compositions and formulations for parenteral, intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and  
15 other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active  
25 ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid  
35 syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated

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as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

In one embodiment of the present invention the pharmaceutical compositions may be formulated and used as foams. Pharmaceutical foams include formulations such as, but not limited to, emulsions, microemulsions, creams, jellies and liposomes. While basically similar in nature these formulations vary in the components and the consistency of the final product. The preparation of such compositions and formulations is generally known to those skilled in the pharmaceutical and formulation arts and may be applied to the formulation of the compositions of the present invention.

#### Emulsions

The compositions of the present invention may be prepared and formulated as emulsions. Emulsions are typically heterogenous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1  $\mu\text{m}$  in diameter (Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi et al., in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions may be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion.

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Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w)

emulsion. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants may also be present in emulsions as needed.

Pharmaceutical emulsions may also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion may be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that may be incorporated into either phase of the emulsion. Emulsifiers may broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (Rieger,

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in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants may be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in *Pharmaceutical Dosage Forms*, Lieberman,

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Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that may readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations via dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker,

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (Rosoff, in *Pharmaceutical Dosage Forms*,

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Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption

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of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (Constantinides et al., *Pharmaceutical Research*, 1994, 11, 1385-1390; Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (Constantinides et al., *Pharmaceutical Research*, 1994, 11, 1385; Ho et al., *J. Pharm. Sci.*, 1996, 85, 138-143). Often microemulsions may form spontaneously when their components are brought together at ambient temperature. This may be particularly advantageous when formulating thermolabile drugs, peptides or oligonucleotides. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of oligonucleotides and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of oligonucleotides and nucleic acids within the gastrointestinal tract, vagina, buccal cavity and other areas of administration.

Microemulsions of the present invention may also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the oligonucleotides and nucleic acids of the present invention. Penetration enhancers used in the microemulsions of the present invention may be classified as belonging to one of five broad categories - surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee et al., *Critical Reviews in Therapeutic*



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*Drug Carrier Systems*, 1991, p. 92). Each of these classes has been discussed above.

#### Liposomes

5        There are many organized surfactant structures besides microemulsions that have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the  
10       duration of action they offer from the standpoint of drug delivery. As used in the present invention, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers.

      Liposomes are unilamellar or multilamellar vesicles  
15       which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composition to be delivered. Cationic liposomes possess the advantage of being able to fuse to the cell wall. Non-cationic liposomes, although not able to fuse as efficiently  
20       with the cell wall, are taken up by macrophages *in vivo*.

      In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. Therefore, it is desirable to use a  
25       liposome which is highly deformable and able to pass through such fine pores.

      Further advantages of liposomes include; liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of  
30       water and lipid soluble drugs; liposomes can protect encapsulated drugs in their internal compartments from metabolism and degradation (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Important  
35       considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

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Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomes start to merge with the cellular membranes and as the merging of the liposome and cell progresses, the liposomal contents are emptied into the cell where the active agent may act.

Liposomal formulations have been the focus of extensive investigation as the mode of delivery for many drugs. There is growing evidence that for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side-effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer a wide variety of drugs, both hydrophilic and hydrophobic, into the skin.

Several reports have detailed the ability of liposomes to deliver agents including high-molecular weight DNA into the skin. Compounds including analgesics, antibodies, hormones and high-molecular weight DNAs have been administered to the skin. The majority of applications resulted in the targeting of the upper epidermis.

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged DNA molecules to form a stable complex. The positively charged DNA/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang et al., *Biochem. Biophys. Res. Commun.*, 1987, 147, 980-985).

Liposomes which are pH-sensitive or negatively-charged, entrap DNA rather than complex with it. Since both the DNA and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some DNA is entrapped within the aqueous interior of these liposomes. pH-sensitive

30 Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-  
35 10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results

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indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporin-A into different layers of the skin (Hu et al. *S.T.P. Pharma. Sci.*, 1994, 4, 6, 466).

5       Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized  
10 lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G<sub>M1</sub>, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol  
15 (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized  
20 liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen et al., *FEBS Letters*, 1987, 223, 42; Wu et al., *Cancer Research*, 1993, 53, 3765).

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos et al. (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of  
25 monosialoganglioside G<sub>M1</sub>, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 1988, 85, 6949). U.S.  
30 Patent No. 4,837,028 and WO 88/04924, both to Allen et al., disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G<sub>M1</sub> or a galactocerebroside sulfate ester. U.S. Patent No. 5,543,152 (Webb et al.) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499  
35 (Lim et al.).

Many liposomes comprising lipids derivatized with one or more hydrophilic polymers, and methods of preparation thereof, are known in the art. Sunamoto et al. (*Bull. Chem. Soc. Jpn.*, **1980**, 53, 2778) described liposomes comprising a nonionic detergent, 2C<sub>12</sub>15G, that contains a PEG moiety. Illum et al. (*FEBS Lett.*, **1984**, 167, 79) noted that hydrophilic coating of polystyrene particles with polymeric glycols results in significantly enhanced blood half-lives. Synthetic phospholipids modified by the attachment of carboxylic groups of polyalkylene glycols (e.g., PEG) are described by Sears (U.S. Patent Nos. 4,426,330 and 4,534,899). Klibanov et al. (*FEBS Lett.*, **1990**, 268, 235) described experiments demonstrating that liposomes comprising phosphatidylethanolamine (PE) derivatized with PEG or PEG stearate have significant increases in blood circulation half-lives. Blume et al. (*Biochimica et Biophysica Acta*, **1990**, 1029, 91) extended such observations to other PEG-derivatized phospholipids, e.g., DSPE-PEG, formed from the combination of distearoylphosphatidylethanolamine (DSPE) and PEG. Liposomes having covalently bound PEG moieties on their external surface are described in European Patent No. EP 0 445 131 B1 and WO 90/04384 to Fisher. Liposome compositions containing 1-20 mole percent of PE derivatized with PEG, and methods of use thereof, are described by Woodle et al. (U.S. Patent Nos. 5,013,556 and 5,356,633) and Martin et al. (U.S. Patent No. 5,213,804 and European Patent No. EP 0 496 813 B1). Liposomes comprising a number of other lipid-polymer conjugates are disclosed in WO 91/05545 and U.S. Patent No. 5,225,212 (both to Martin et al.) and in WO 94/20073 (Zalipsky et al.) Liposomes comprising PEG-modified ceramide lipids are described in WO 96/10391 (Choi et al.). U.S. Patent Nos. 5,540,935 (Miyazaki et al.) and 5,556,948 (Tagawa et al.) describe PEG-containing liposomes that can be further derivatized with functional moieties on their surfaces.

A limited number of liposomes comprising nucleic acids are known in the art. WO 96/40062 to Thierry et al. discloses methods for encapsulating high molecular weight

35        If the surfactant molecule is not ionized, it is  
classified as a nonionic surfactant. Nonionic surfactants  
find wide application in pharmaceutical and cosmetic products

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and are usable over a wide range of pH values. In general their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl  
5 esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most  
10 popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of  
15 amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and  
20 the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The  
25 quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include  
30 acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, NY, 1988, p.  
35 285).

Penetration Enhancers

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In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly oligonucleotides, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92). Each of the above mentioned classes of penetration enhancers are described below in greater detail.

Surfactants: In connection with the present invention, surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of oligonucleotides through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi et al., *J. Pharm. Pharmacol.*, 1988, 40, 252).

Fatty acids: Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprates, tricaprates, monoolein (1-



Bile salts: The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (Brunton, Chapter 38 in: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed., Hardman et al. Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. The bile salts of the invention include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucolic acid (sodium glucolate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Swinyard, Chapter 39 In: *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA, 1990, pages 782-783; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990,

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7, 1-33; Yamamoto et al., *J. Pharm. Exp. Ther.*, **1992**, 263, 25; Yamashita et al., *J. Pharm. Sci.*, **1990**, 79, 579-583).

Chelating Agents: Chelating agents, as used in connection with the present invention, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of oligonucleotides through the mucosa is enhanced. With regards to their use as penetration enhancers in the present invention, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, *J. Chromatogr.*, **1993**, 618, 315-339). Chelating agents of the invention include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (e.g., sodium salicylate, 5-methoxysalicylate and homovanilate), *N*-acyl derivatives of collagen, laureth-9 and *N*-amino acyl derivatives of beta-diketones (enamines) (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, **1991**, page 92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, **1990**, 7, 1-33; Buur et al., *J. Control Rel.*, **1990**, 14, 43-51).

Non-chelating non-surfactants: As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of oligonucleotides through the alimentary mucosa (Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, **1990**, 7, 1-33). This class of penetration enhancers include, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, **1991**, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin

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and phenylbutazone (Yamashita et al., *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

Agents that enhance uptake of oligonucleotides at the cellular level may also be added to the pharmaceutical and other compositions of the present invention. For example, cationic lipids, such as lipofectin (Junichi et al, U.S. Patent No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo et al., PCT Application WO 97/30731), are also known to enhance the cellular uptake of oligonucleotides.

Other agents may be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

15

#### Carriers

Certain compositions of the present invention also incorporate carrier compounds in the formulation. As used herein, "carrier compound" or "carrier" can refer to a nucleic acid, or analog thereof, which is inert (i.e., does not possess biological activity *per se*) but is recognized as a nucleic acid by *in vivo* processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate oligonucleotide in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'-isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., *Antisense Res. Dev.*, 1995, 5,

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115-121; Takakura *et al.*, *Antisense & Nucl. Acid Drug Dev.*, 1996, 6, 177-183).

#### Excipients

5 In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient may be liquid or solid and is  
10 selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents  
15 (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, etc.); fillers (e.g., lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, etc.); lubricants (e.g.,  
20 magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, etc.); disintegrants (e.g., starch, sodium starch glycolate, etc.); and wetting agents (e.g., sodium  
25 lauryl sulphate, etc.).

Pharmaceutically acceptable organic or inorganic excipient suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present invention.  
30 Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

35 Formulations for topical administration of nucleic acids may include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or

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solutions of the nucleic acids in liquid or solid oil bases. The solutions may also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral  
5 administration which do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium  
10 stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

#### Other Components

The compositions of the present invention may  
15 additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example,  
20 antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers,  
25 thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants,  
30 preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

35 Aqueous suspensions may contain substances which increase the viscosity of the suspension including, for

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example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more  
5 antisense compounds and (b) one or more other chemotherapeutic agents which function by a non-antisense mechanism. Examples of such chemotherapeutic agents include but are not limited to daunorubicin, daunomycin, dactinomycin, doxorubicin, epirubicin, idarubicin,  
10 esorubicin, bleomycin, mafosfamide, ifosfamide, cytosine, arabinoside, bis-chloroethylnitrosurea, busulfan, mitomycin C, actinomycin D, mithramycin, prednisone, hydroxyprogesterone, testosterone, tamoxifen, dacarbazine, procarbazine, hexamethylmelamine, pentamethylmelamine,  
15 mitoxantrone, amsacrine, chlorambucil, methylcyclohexylnitrosurea, nitrogen mustards, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-azacytidine, hydroxyurea, deoxycoformycin, 4-hydroxyperoxycyclophosphoramidate, 5-fluorouracil (5-FU), 5-  
20 fluorodeoxyuridine (5-FUdR), methotrexate (MTX), colchicine, taxol, vincristine, vinblastine, etoposide (VP-16), trimetrexate, irinotecan, topotecan, gemcitabine, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, *The Merck Manual of Diagnosis and Therapy*, 15th Ed. 1987, pp.  
25 1206-1228, Berkow et al., eds., Rahway, N.J. When used with the compounds of the invention, such chemotherapeutic agents may be used individually (e.g., 5-FU and oligonucleotide), sequentially (e.g., 5-FU and oligonucleotide for a period of time followed by MTX and oligonucleotide), or in combination  
30 with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide, or 5-FU, radiotherapy and oligonucleotide). Anti-inflammatory drugs, including but not limited to nonsteroidal anti-inflammatory drugs and corticosteroids, and antiviral drugs, including but not  
35 limited to ribivirin, vidarabine, acyclovir and ganciclovir, may also be combined in compositions of the invention. See, generally, *The Merck Manual of Diagnosis and Therapy*, 15th

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Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). Other non-antisense chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used  
5 together or sequentially.

In another related embodiment, compositions of the invention may contain one or more antisense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional antisense compounds targeted  
10 to a second nucleic acid target. Numerous examples of antisense compounds are known in the art. Two or more combined compounds may be used together or sequentially.

The formulation of therapeutic compositions and their subsequent administration is believed to be within the skill  
15 of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be  
20 calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can  
25 generally be estimated based on  $EC_{50}$ s found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 ug to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art  
30 can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state,  
35 wherein the oligonucleotide is administered in maintenance doses, ranging from 0.01 ug to 100 g per kg of body weight, once or more daily, to once every 20 years.

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While the present invention has been described with specificity in accordance with certain of its preferred embodiments, the following examples serve only to illustrate the invention and are not intended to limit the same.



**EXAMPLES****Example 1****5 Nucleoside Phosphoramidites for Oligonucleotide Synthesis  
Deoxy and 2'-alkoxy amidites**

2'-Deoxy and 2'-methoxy beta-cyanoethyldiisopropyl phosphoramidites were purchased from commercial sources (e.g. Chemgenes, Needham MA or Glen Research, Inc. Sterling VA).  
10 Other 2'-O-alkoxy substituted nucleoside amidites are prepared as described in U.S. Patent 5,506,351, herein incorporated by reference. For oligonucleotides synthesized using 2'-alkoxy amidites, optimized synthesis cycles were developed that incorporate multiple steps coupling longer  
15 wait times relative to standard synthesis cycles.

The following abbreviations are used in the text: thin layer chromatography (TLC), melting point (MP), high pressure liquid chromatography (HPLC), Nuclear Magnetic Resonance (NMR), argon (Ar), methanol (MeOH), dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>),  
20 triethylamine (TEA), dimethyl formamide (DMF), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF).

Oligonucleotides containing 5-methyl-2'-deoxycytidine (5-Me-dC) nucleotides were synthesized according to published methods (Sanghvi, et. al., *Nucleic Acids Research*, 1993, 21,  
25 3197-3203) using commercially available phosphoramidites (Glen Research, Sterling VA or ChemGenes, Needham MA) or prepared as follows:

**30 Preparation of 5'-O-Dimethoxytrityl-thymidine intermediate  
for 5-methyl dC amidite**

To a 50 L glass reactor equipped with air stirrer and Ar gas line was added thymidine (1.00 kg, 4.13 mol) in anhydrous pyridine (6 L) at ambient temperature. Dimethoxytrityl (DMT) chloride (1.47 kg, 4.34 mol, 1.05 eq) was added as a solid in  
35 four portions over 1 h. After 30 min, TLC indicated approx. 95% product, 2% thymidine, 5% DMT reagent and by-products and 2 % 3',5'-bis DMT product (R<sub>f</sub> in EtOAc 0.45, 0.05, 0.98, 0.95

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respectively). Saturated sodium bicarbonate (4 L) and  $\text{CH}_2\text{Cl}_2$  were added with stirring (pH of the aqueous layer 7.5). An additional 18 L of water was added, the mixture was stirred, the phases were separated, and the organic layer was transferred to a second 50 L vessel. The aqueous layer was extracted with additional  $\text{CH}_2\text{Cl}_2$  (2 x 2 L). The combined organic layer was washed with water (10 L) and then concentrated in a rotary evaporator to approx. 3.6 kg total weight. This was redissolved in  $\text{CH}_2\text{Cl}_2$  (3.5 L), added to the reactor followed by water (6 L) and hexanes (13 L). The mixture was vigorously stirred and seeded to give a fine white suspended solid starting at the interface. After stirring for 1 h, the suspension was removed by suction through a 1/2" diameter teflon tube into a 20 L suction flask, poured onto a 25 cm Coors Buchner funnel, washed with water (2 x 3 L) and a mixture of hexanes-  $\text{CH}_2\text{Cl}_2$  (4:1, 2x3 L) and allowed to air dry overnight in pans (1" deep). This was further dried in a vacuum oven (75°C, 0.1 mm Hg, 48 h) to a constant weight of 2072 g (93%) of a white solid, (mp 122-124°C). TLC indicated a trace contamination of the bis DMT product. NMR spectroscopy also indicated that 1-2 mole percent pyridine and about 5 mole percent of hexanes was still present.

**25 Preparation of 5'-O-Dimethoxytrityl-2'-deoxy-5-methylcytidine intermediate for 5-methyl-dC amidite**

To a 50 L Schott glass-lined steel reactor equipped with an electric stirrer, reagent addition pump (connected to an addition funnel), heating/cooling system, internal thermometer and an Ar gas line was added 5'-O-dimethoxytrityl-thymidine (3.00 kg, 5.51 mol), anhydrous acetonitrile (25 L) and TEA (12.3 L, 88.4 mol, 16 eq). The mixture was chilled with stirring to -10°C internal temperature (external -20°C). Trimethylsilylchloride (2.1 L, 16.5 mol, 3.0 eq) was added over 30 minutes while maintaining the internal temperature below -5°C, followed by a wash of anhydrous acetonitrile (1 L). Note: the reaction is mildly

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exothermic and copious hydrochloric acid fumes form over the course of the addition. The reaction was allowed to warm to 0°C and the reaction progress was confirmed by TLC (EtOAc-hexanes 4:1;  $R_f$  0.43 to 0.84 of starting material and silyl product, respectively). Upon completion, triazole (3.05 kg, 44 mol, 8.0 eq) was added the reaction was cooled to -20°C internal temperature (external -30°C). Phosphorous oxychloride (1035 mL, 11.1 mol, 2.01 eq) was added over 60 min so as to maintain the temperature between -20°C and -10°C during the strongly exothermic process, followed by a wash of anhydrous acetonitrile (1 L). The reaction was warmed to 0°C and stirred for 1 h. TLC indicated a complete conversion to the triazole product ( $R_f$  0.83 to 0.34 with the product spot glowing in long wavelength UV light). The reaction mixture was a peach-colored thick suspension, which turned darker red upon warming without apparent decomposition. The reaction was cooled to -15°C internal temperature and water (5 L) was slowly added at a rate to maintain the temperature below +10°C in order to quench the reaction and to form a homogenous solution. (Caution: this reaction is initially very strongly exothermic). Approximately one-half of the reaction volume (22 L) was transferred by air pump to another vessel, diluted with EtOAc (12 L) and extracted with water (2 x 8 L). The combined water layers were back-extracted with EtOAc (6 L). The water layer was discarded and the organic layers were concentrated in a 20 L rotary evaporator to an oily foam. The foam was coevaporated with anhydrous acetonitrile (4 L) to remove EtOAc. (note: dioxane may be used instead of anhydrous acetonitrile if dried to a hard foam). The second half of the reaction was treated in the same way. Each residue was dissolved in dioxane (3 L) and concentrated ammonium hydroxide (750 mL) was added. A homogenous solution formed in a few minutes and the reaction was allowed to stand overnight (although the reaction is complete within 1 h).

TLC indicated a complete reaction (product  $R_f$  0.35 in EtOAc-MeOH 4:1). The reaction solution was concentrated on a

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rotary evaporator to a dense foam. Each foam was slowly redissolved in warm EtOAc (4 L; 50°C), combined in a 50 L glass reactor vessel, and extracted with water (2 x 4L) to remove the triazole by-product. The water was back-extracted with EtOAc (2 L). The organic layers were combined and concentrated to about 8 kg total weight, cooled to 0°C and seeded with crystalline product. After 24 hours, the first crop was collected on a 25 cm Coors Buchner funnel and washed repeatedly with EtOAc (3 x 3L) until a white powder was left and then washed with ethyl ether (2 x 3L). The solid was put in pans (1" deep) and allowed to air dry overnight. The filtrate was concentrated to an oil, then redissolved in EtOAc (2 L), cooled and seeded as before. The second crop was collected and washed as before (with proportional solvents) and the filtrate was first extracted with water (2 x 1L) and then concentrated to an oil. The residue was dissolved in EtOAc (1 L) and yielded a third crop which was treated as above except that more washing was required to remove a yellow oily layer.

After air-drying, the three crops were dried in a vacuum oven (50°C, 0.1 mm Hg, 24 h) to a constant weight (1750, 600 and 200 g, respectively) and combined to afford 2550 g (85%) of a white crystalline product (MP 215-217°C) when TLC and NMR spectroscopy indicated purity. The mother liquor still contained mostly product (as determined by TLC) and a small amount of triazole (as determined by NMR spectroscopy), bis DMT product and unidentified minor impurities. If desired, the mother liquor can be purified by silica gel chromatography using a gradient of MeOH (0-25%) in EtOAc to further increase the yield.

**Preparation of 5'-O-Dimethoxytrityl-2'-deoxy-N<sup>4</sup>-benzoyl-5-methylcytidine penultimate intermediate for 5-methyl dC amidite**

Crystalline 5'-O-dimethoxytrityl-5-methyl-2'-deoxycytidine (2000 g, 3.68 mol) was dissolved in anhydrous DMF (6.0 kg) at ambient temperature in a 50 L glass reactor

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vessel equipped with an air stirrer and argon line. Benzoic anhydride (Chem Impex not Aldrich, 874 g, 3.86 mol, 1.05 eq) was added and the reaction was stirred at ambient temperature for 8 h. TLC ( $\text{CH}_2\text{Cl}_2$ -EtOAc;  $\text{CH}_2\text{Cl}_2$ -EtOAc 4:1;  $R_f$  0.25)

5 indicated approx. 92% complete reaction. An additional amount of benzoic anhydride (44 g, 0.19 mol) was added. After a total of 18 h, TLC indicated approx. 96% reaction completion. The solution was diluted with EtOAc (20 L), TEA (1020 mL, 7.36 mol, ca 2.0 eq) was added with stirring, and  
10 the mixture was extracted with water (15 L, then 2 x 10 L). The aqueous layer was removed (no back-extraction was needed) and the organic layer was concentrated in 2 x 20 L rotary evaporator flasks until a foam began to form. The residues were coevaporated with acetonitrile (1.5 L each) and dried  
15 (0.1 mm Hg, 25°C, 24 h) to 2520 g of a dense foam. High pressure liquid chromatography (HPLC) revealed a contamination of 6.3% of N4, 3'-O-dibenzoyl product, but very little other impurities.

The product was purified by Biotage column  
20 chromatography (5 kg Biotage) prepared with 65:35:1 hexanes-EtOAc-TEA (4L). The crude product (800 g), dissolved in  $\text{CH}_2\text{Cl}_2$  (2 L), was applied to the column. The column was washed with the 65:35:1 solvent mixture (20 kg), then 20:80:1 solvent mixture (10 kg), then 99:1 EtOAc:TEA (17kg). The fractions  
25 containing the product were collected, and any fractions containing the product and impurities were retained to be resubjected to column chromatography. The column was re-equilibrated with the original 65:35:1 solvent mixture (17 kg). A second batch of crude product (840 g) was applied to  
30 the column as before. The column was washed with the following solvent gradients: 65:35:1 (9 kg), 55:45:1 (20 kg), 20:80:1 (10 kg), and 99:1 EtOAc:TEA (15 kg). The column was reequilibrated as above, and a third batch of the crude product (850 g) plus impure fractions recycled from the two  
35 previous columns (28 g) was purified following the procedure for the second batch. The fractions containing pure product combined and concentrated on a 20L rotary evaporator, co-

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evaporated with acetontirile (3 L) and dried (0.1 mm Hg, 48 h, 25°C) to a constant weight of 2023 g (85%) of white foam and 20 g of slightly contaminated product from the third run. HPLC indicated a purity of 99.8% with the balance as the diBenzoyl product.

**[5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-deoxy-N<sup>4</sup>-benzoyl-5-methylcytidin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (5-methyl dC amidite)**

5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-deoxy-N<sup>4</sup>-benzoyl-5-methylcytidine (998 g, 1.5 mol) was dissolved in anhydrous DMF (2 L). The solution was co-evaporated with toluene (300 ml) at 50°C under reduced pressure, then cooled to room temperature and 2-cyanoethyl tetraisopropylphosphorodiamidite (680 g, 2.26 mol) and tetrazole (52.5 g, 0.75 mol) were added. The mixture was shaken until all tetrazole was dissolved, N-methylimidazole (15 ml) was added and the mixture was left at room temperature for 5 hours. TEA (300 ml) was added, the mixture was diluted with DMF (2.5 L) and water (600 ml), and extracted with hexane (3 x 3 L). The mixture was diluted with water (1.2 L) and extracted with a mixture of toluene (7.5 L) and hexane (6 L). The two layers were separated, the upper layer was washed with DMF-water (7:3 v/v, 3 x 2 L) and water (3 x 2 L), and the phases were separated. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and rotary evaporated. The residue was co-evaporated with acetonitrile (2 x 2 L) under reduced pressure and dried to a constant weight (25 °C, 0.1mm Hg, 40 h) to afford 1250 g an off-white foam solid (96%).

### 2'-Fluoro amidites

#### 2'-Fluorodeoxyadenosine amidites

2'-fluoro oligonucleotides were synthesized as described previously [Kawasaki, et. al., *J. Med. Chem.*, 1993, 36, 831-841] and United States patent 5,670,633, herein incorporated by reference. The preparation of 2'-fluoropyrimidines containing a 5-methyl substitution are described in US Patent

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5,861,493. Briefly, the protected nucleoside N6-benzoyl-2'-deoxy-2'-fluoroadenosine was synthesized utilizing commercially available 9-beta-D-arabinofuranosyladenine as starting material and whereby the 2'-alpha-fluoro atom is introduced by a S<sub>N</sub>2-displacement of a 2'-beta-triflate group. Thus N6-benzoyl-9-beta-D-arabinofuranosyladenine was selectively protected in moderate yield as the 3',5'-ditetrahydropyranyl (THP) intermediate. Deprotection of the THP and N6-benzoyl groups was accomplished using standard methodologies to obtain the 5'-dimethoxytrityl-(DMT) and 5'-DMT-3'-phosphoramidite intermediates.

#### 2'-Fluorodeoxyguanosine

The synthesis of 2'-deoxy-2'-fluoroguanosine was accomplished using tetraisopropylidisiloxanyl (TPDS) protected 9-beta-D-arabinofuranosylguanine as starting material, and conversion to the intermediate isobutyryl-arabinofuranosylguanosine. Alternatively, isobutyryl-arabinofuranosylguanosine was prepared as described by Ross et al., (Nucleosides & Nucleosides, 16, 1645, 1997). Deprotection of the TPDS group was followed by protection of the hydroxyl group with THP to give isobutyryl di-THP protected arabinofuranosylguanine. Selective O-deacylation and triflation was followed by treatment of the crude product with fluoride, then deprotection of the THP groups. Standard methodologies were used to obtain the 5'-DMT- and 5'-DMT-3'-phosphoramidites.

#### 2'-Fluorouridine

Synthesis of 2'-deoxy-2'-fluorouridine was accomplished by the modification of a literature procedure in which 2,2'-anhydro-1-beta-D-arabinofuranosyluracil was treated with 70% hydrogen fluoride-pyridine. Standard procedures were used to obtain the 5'-DMT and 5'-DMT-3'phosphoramidites.

#### 2'-Fluorodeoxycytidine

2'-deoxy-2'-fluorocytidine was synthesized via amination

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of 2'-deoxy-2'-fluorouridine, followed by selective protection to give N4-benzoyl-2'-deoxy-2'-fluorocytidine. Standard procedures were used to obtain the 5'-DMT and 5'-DMT-3'phosphoramidites.

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# **2'-O-(2-Methoxyethyl) modified amidites**

2'-O-Methoxyethyl-substituted nucleoside amidites (otherwise known as MOE amidites) are prepared as follows, or alternatively, as per the methods of Martin, P., (Helvetica Chimica Acta, 1995, 78, 486-504).

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## **Preparation of 2'-O-(2-methoxyethyl)-5-methyluridine intermediate**

2,2'-Anhydro-5-methyl-uridine (2000 g, 8.32 mol), tris(2-methoxyethyl)borate (2504 g, 10.60 mol), sodium bicarbonate (60 g, 0.70 mol) and anhydrous 2-methoxyethanol (5 L) were combined in a 12 L three necked flask and heated to 130 °C (internal temp) at atmospheric pressure, under an argon atmosphere with stirring for 21 h. TLC indicated a complete reaction. The solvent was removed under reduced pressure until a sticky gum formed (50-85°C bath temp and 100-11 mm Hg) and the residue was redissolved in water (3 L) and heated to boiling for 30 min in order the hydrolyze the borate esters. The water was removed under reduced pressure until a foam began to form and then the process was repeated. HPLC indicated about 77% product, 15% dimer (5' of product attached to 2' of starting material) and unknown derivatives, and the balance was a single unresolved early eluting peak.

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The gum was redissolved in brine (3 L), and the flask was rinsed with additional brine (3 L). The combined aqueous solutions were extracted with chloroform (20 L) in a heavier-than continuous extractor for 70 h. The chloroform layer was concentrated by rotary evaporation in a 20 L flask to a sticky foam (2400 g). This was coevaporated with MeOH (400 mL) and EtOAc (8 L) at 75°C and 0.65 atm until the foam dissolved at which point the vacuum was lowered to about 0.5 atm. After 2.5 L of distillate was collected a precipitate

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began to form and the flask was removed from the rotary evaporator and stirred until the suspension reached ambient temperature. EtOAc (2 L) was added and the slurry was filtered on a 25 cm table top Buchner funnel and the product was washed with EtOAc (3 x 2 L). The bright white solid was air dried in pans for 24 h then further dried in a vacuum oven (50°C, 0.1 mm Hg, 24 h) to afford 1649 g of a white crystalline solid (mp 115.5-116.5°C).

The brine layer in the 20 L continuous extractor was further extracted for 72 h with recycled chloroform. The chloroform was concentrated to 120 g of oil and this was combined with the mother liquor from the above filtration (225 g), dissolved in brine (250 mL) and extracted once with chloroform (250 mL). The brine solution was continuously extracted and the product was crystallized as described above to afford an additional 178 g of crystalline product containing about 2% of thymine. The combined yield was 1827 g (69.4%). HPLC indicated about 99.5% purity with the balance being the dimer.

#### Preparation of 5'-O-DMT-2'-O-(2-methoxyethyl)-5-methyluridine penultimate intermediate

In a 50 L glass-lined steel reactor, 2'-O-(2-methoxyethyl)-5-methyl-uridine (MOE-T, 1500 g, 4.738 mol), lutidine (1015 g, 9.476 mol) were dissolved in anhydrous acetonitrile (15 L). The solution was stirred rapidly and chilled to -10°C (internal temperature). Dimethoxytriphenylmethyl chloride (1765.7 g, 5.21 mol) was added as a solid in one portion. The reaction was allowed to warm to -2°C over 1 h. (Note: The reaction was monitored closely by TLC (EtOAc) to determine when to stop the reaction so as to not generate the undesired bis-DMT substituted side product). The reaction was allowed to warm from -2 to 3°C over 25 min. then quenched by adding MeOH (300 mL) followed after 10 min by toluene (16 L) and water (16 L). The solution was transferred to a clear 50 L vessel with a bottom outlet, vigorously stirred for 1 minute, and the layers

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separated. The aqueous layer was removed and the organic layer was washed successively with 10% aqueous citric acid (8 L) and water (12 L). The product was then extracted into the aqueous phase by washing the toluene solution with aqueous sodium hydroxide (0.5N, 16 L and 8 L). The combined aqueous layer was overlayed with toluene (12 L) and solid citric acid (8 moles, 1270 g) was added with vigorous stirring to lower the pH of the aqueous layer to 5.5 and extract the product into the toluene. The organic layer was washed with water (10 L) and TLC of the organic layer indicated a trace of DMT-O-Me, bis DMT and dimer DMT.

The toluene solution was applied to a silica gel column (6 L sintered glass funnel containing approx. 2 kg of silica gel slurried with toluene (2 L) and TEA(25 mL)) and the fractions were eluted with toluene (12 L) and EtOAc (3 x 4 L) using vacuum applied to a filter flask placed below the column. The first EtOAc fraction containing both the desired product and impurities were resubjected to column chromatography as above. The clean fractions were combined, rotary evaporated to a foam, coevaporated with acetonitrile (6 L) and dried in a vacuum oven (0.1 mm Hg, 40 h, 40°C) to afford 2850 g of a white crisp foam. NMR spectroscopy indicated a 0.25 mole % remainder of acetonitrile (calculates to be approx. 47 g) to give a true dry weight of 2803 g (96%). HPLC indicated that the product was 99.41% pure, with the remainder being 0.06 DMT-O-Me, 0.10 unknown, 0.44 bis DMT, and no detectable dimer DMT or 3'-O-DMT.

**Preparation of [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-5-methyluridin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE T amidite)**

5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-5-methyluridine (1237 g, 2.0 mol) was dissolved in anhydrous DMF (2.5 L). The solution was co-evaporated with toluene (200 ml) at 50°C under reduced pressure, then cooled to room temperature and 2-cyanoethyl tetraisopropylphosphorodiamidite (900 g, 3.0 mol) and

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tetrazole (70 g, 1.0 mol) were added. The mixture was shaken until all tetrazole was dissolved, N-methylimidazole (20 ml) was added and the solution was left at room temperature for 5 hours. TEA (300 ml) was added, the mixture was diluted with 5 DMF (3.5 L) and water (600 ml) and extracted with hexane (3 x 3L). The mixture was diluted with water (1.6 L) and extracted with the mixture of toluene (12 L) and hexanes (9 L). The upper layer was washed with DMF-water (7:3 v/v, 3x3 L) and water (3x3 L). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered 10 and evaporated. The residue was co-evaporated with acetonitrile (2 x 2 L) under reduced pressure and dried in a vacuum oven (25°C, 0.1mm Hg, 40 h) to afford 1526 g of an off-white foamy solid (95%).

1:5 **Preparation of 5'-O-Dimethoxytrityl-2'-O-(2-methoxyethyl)-5-methylcytidine intermediate**

To a 50 L Schott glass-lined steel reactor equipped with an electric stirrer, reagent addition pump (connected to an addition funnel), heating/cooling system, internal 20 thermometer and argon gas line was added 5'-O-dimethoxytrityl-2'-O-(2-methoxyethyl)-5-methyl-uridine (2.616 kg, 4.23 mol, purified by base extraction only and no scrub column), anhydrous acetonitrile (20 L), and TEA (9.5 L, 67.7 mol, 16 eq). The mixture was chilled with stirring to -10°C 25 internal temperature (external -20°C). Trimethylsilylchloride (1.60 L, 12.7 mol, 3.0 eq) was added over 30 min. while maintaining the internal temperature below -5°C, followed by a wash of anhydrous acetonitrile (1 L). (Note: the reaction is mildly exothermic and copious 30 hydrochloric acid fumes form over the course of the addition). The reaction was allowed to warm to 0°C and the reaction progress was confirmed by TLC (EtOAc,  $R_f$  0.68 and 0.87 for starting material and silyl product, respectively). Upon completion, triazole (2.34 kg, 33.8 mol, 8.0 eq) was 35 added the reaction was cooled to -20°C internal temperature (external -30°C). Phosphorous oxychloride (793 mL, 8.51 mol, 2.01 eq) was added slowly over 60 min so as to maintain the

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temperature between  $-20^{\circ}\text{C}$  and  $-10^{\circ}\text{C}$  (note: strongly exothermic), followed by a wash of anhydrous acetonitrile (1 L). The reaction was warmed to  $0^{\circ}\text{C}$  and stirred for 1 h, at which point it was an off-white thick suspension. TLC indicated a complete conversion to the triazole product (EtOAc,  $R_f$  0.87 to 0.75 with the product spot glowing in long wavelength UV light). The reaction was cooled to  $-15^{\circ}\text{C}$  and water (5 L) was slowly added at a rate to maintain the temperature below  $+10^{\circ}\text{C}$  in order to quench the reaction and to form a homogenous solution. (Caution: this reaction is initially very strongly exothermic). Approximately one-half of the reaction volume (22 L) was transferred by air pump to another vessel, diluted with EtOAc (12 L) and extracted with water (2 x 8 L). The second half of the reaction was treated in the same way. The combined aqueous layers were back-extracted with EtOAc (8 L). The organic layers were combined and concentrated in a 20 L rotary evaporator to an oily foam. The foam was coevaporated with anhydrous acetonitrile (4 L) to remove EtOAc. (note: dioxane may be used instead of anhydrous acetonitrile if dried to a hard foam). The residue was dissolved in dioxane (2 L) and concentrated ammonium hydroxide (750 mL) was added. A homogenous solution formed in a few minutes and the reaction was allowed to stand overnight.

TLC indicated a complete reaction ( $\text{CH}_2\text{Cl}_2$ -acetone-MeOH, 20:5:3,  $R_f$  0.51). The reaction solution was concentrated on a rotary evaporator to a dense foam and slowly redissolved in warm  $\text{CH}_2\text{Cl}_2$  (4 L,  $40^{\circ}\text{C}$ ) and transferred to a 20 L glass extraction vessel equipped with a air-powered stirrer. The organic layer was extracted with water (2 x 6 L) to remove the triazole by-product. (Note: In the first extraction an emulsion formed which took about 2 h to resolve). The water layer was back-extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 2 L), which in turn was washed with water (3 L). The combined organic layer was concentrated in 2 x 20 L flasks to a gum and then recrystallized from EtOAc seeded with crystalline product. After sitting overnight, the first crop was collected on a 25

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cm Coors Buchner funnel and washed repeatedly with EtOAc until a white free-flowing powder was left (about 3 x 3 L). The filtrate was concentrated to an oil recrystallized from EtOAc, and collected as above. The solid was air-dried in  
5 pans for 48 h, then further dried in a vacuum oven (50°C, 0.1mm Hg, 17 h) to afford 2248 g of a bright white, dense solid (86%). An HPLC analysis indicated both crops to be 99.4% pure and NMR spectroscopy indicated only a faint trace of EtOAc remained.

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**Preparation of 5'-O-dimethoxytrityl-2'-O-(2-methoxyethyl)-N4-benzoyl-5-methyl-cytidine penultimate intermediate:**

Crystalline 5'-O-dimethoxytrityl-2'-O-(2-methoxyethyl)-5-methyl-cytidine (1000 g, 1.62 mol) was suspended in  
15 anhydrous DMF (3 kg) at ambient temperature and stirred under an Ar atmosphere. Benzoic anhydride (439.3 g, 1.94 mol) was added in one portion. The solution clarified after 5 hours and was stirred for 16 h. HPLC indicated 0.45% starting material remained (as well as 0.32% N4, 3'-O-bis Benzoyl).  
20 An additional amount of benzoic anhydride (6.0 g, 0.0265 mol) was added and after 17 h, HPLC indicated no starting material was present. TEA (450 mL, 3.24 mol) and toluene (6 L) were added with stirring for 1 minute. The solution was washed with water (4 x 4 L), and brine (2 x 4 L). The organic layer  
25 was partially evaporated on a 20 L rotary evaporator to remove 4 L of toluene and traces of water. HPLC indicated that the bis benzoyl side product was present as a 6% impurity. The residue was diluted with toluene (7 L) and anhydrous DMSO (200 mL, 2.82 mol) and sodium hydride (60% in  
30 oil, 70 g, 1.75 mol) was added in one portion with stirring at ambient temperature over 1 h. The reaction was quenched by slowly adding then washing with aqueous citric acid (10%, 100 mL over 10 min, then 2 x 4 L), followed by aqueous sodium bicarbonate (2%, 2 L), water (2 x 4 L) and brine (4 L). The  
35 organic layer was concentrated on a 20 L rotary evaporator to about 2 L total volume. The residue was purified by silica gel column chromatography (6 L Buchner funnel containing 1.5

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kg of silica gel wetted with a solution of EtOAc-hexanes-TEA(70:29:1)). The product was eluted with the same solvent (30 L) followed by straight EtOAc (6 L). The fractions containing the product were combined, concentrated on a rotary evaporator to a foam and then dried in a vacuum oven (50°C, 0.2 mm Hg, 8 h) to afford 1155 g of a crisp, white foam (98%). HPLC indicated a purity of >99.7%.

**Preparation of [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N<sup>4</sup>-benzoyl-5-methylcytidin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE 5-Me-C amidite)**

5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N<sup>4</sup>-benzoyl-5-methylcytidine (1082 g, 1.5 mol) was dissolved in anhydrous DMF (2 L) and co-evaporated with toluene (300 ml) at 50 °C under reduced pressure. The mixture was cooled to room temperature and 2-cyanoethyl tetraisopropylphosphorodiamidite (680 g, 2.26 mol) and tetrazole (52.5 g, 0.75 mol) were added. The mixture was shaken until all tetrazole was dissolved, N-methylimidazole (30 ml) was added, and the mixture was left at room temperature for 5 hours. TEA (300 ml) was added, the mixture was diluted with DMF (1 L) and water (400 ml) and extracted with hexane (3 x 3 L). The mixture was diluted with water (1.2 L) and extracted with a mixture of toluene (9 L) and hexanes (6 L). The two layers were separated and the upper layer was washed with DMF-water (60:40 v/v, 3 x 3 L) and water (3 x 2 L). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was co-evaporated with acetonitrile (2 x 2 L) under reduced pressure and dried in a vacuum oven (25 °C, 0.1mm Hg, 40 h) to afford 1336 g of an off-white foam (97%).

**Preparation of [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N<sup>6</sup>-benzoyl-adenosin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE A amidite)**

5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N<sup>6</sup>-benzoyl-adenosine (purchased from Reliable

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Biopharmaceutical, St. Lois, MO), 1098 g, 1.5 mol) was dissolved in anhydrous DMF (3 L) and co-evaporated with toluene (300 ml) at 50 °C. The mixture was cooled to room temperature and 2-cyanoethyl tetraisopropylphosphorodiamidite (680 g, 2.26 mol) and tetrazole (78.8 g, 1.24 mol) were added. The mixture was shaken until all tetrazole was dissolved, N-methylimidazole (30 ml) was added, and mixture was left at room temperature for 5 hours. TEA (300 ml) was added, the mixture was diluted with DMF (1 L) and water (400 ml) and extracted with hexanes (3 x 3 L). The mixture was diluted with water (1.4 L) and extracted with the mixture of toluene (9 L) and hexanes (6 L). The two layers were separated and the upper layer was washed with DMF-water (60:40, v/v, 3 x 3 L) and water (3 x 2 L). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to a sticky foam. The residue was co-evaporated with acetonitrile (2.5 L) under reduced pressure and dried in a vacuum oven (25 °C, 0.1mm Hg, 40 h) to afford 1350 g of an off-white foam solid (96%).

20      **Preparation of [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N<sup>4</sup>-isobutyrylguanosin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE G amidite)**

5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N<sup>4</sup>-isobutyrylguanosine (purchased from Reliable Biopharmaceutical, St. Louis, MO, 1426 g, 2.0 mol) was dissolved in anhydrous DMF (2 L). The solution was co-evaporated with toluene (200 ml) at 50 °C, cooled to room temperature and 2-cyanoethyl tetraisopropylphosphorodiamidite (900 g, 3.0 mol) and tetrazole (68 g, 0.97 mol) were added. The mixture was shaken until all tetrazole was dissolved, N-methylimidazole (30 ml) was added, and the mixture was left at room temperature for 5 hours. TEA (300 ml) was added, the mixture was diluted with DMF (2 L) and water (600 ml) and extracted with hexanes (3 x 3 L). The mixture was diluted with water (2 L) and extracted with a mixture of toluene (10 L) and hexanes (5 L). The two layers were separated and the upper layer was washed with DMF-water (60:40, v/v, 3x3 L).

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EtOAc (4 L) was added and the solution was washed with water (3 x 4 L). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to approx. 4 kg. Hexane (4 L) was added, the mixture was shaken for 10 min, and the supernatant liquid was  
5 decanted. The residue was co-evaporated with acetonitrile (2 x 2 L) under reduced pressure and dried in a vacuum oven (25 °C, 0.1mm Hg, 40 h) to afford 1660 g of an off-white foamy solid (91%).

10 **2'-O-(Aminooxyethyl) nucleoside amidites and 2'-O-(dimethylaminooxyethyl) nucleoside amidites**

**2'-(Dimethylaminooxyethoxy) nucleoside amidites**

2'-(Dimethylaminooxyethoxy) nucleoside amidites (also known in the art as 2'-O-(dimethylaminooxyethyl) nucleoside  
15 amidites) are prepared as described in the following paragraphs. Adenosine, cytidine and guanosine nucleoside amidites are prepared similarly to the thymidine (5-methyluridine) except the exocyclic amines are protected with a benzoyl moiety in the case of adenosine and cytidine and  
20 with isobutyryl in the case of guanosine.

**5'-O-tert-Butyldiphenylsilyl-O<sup>2</sup>-2'-anhydro-5-methyluridine**

O<sup>2</sup>-2'-anhydro-5-methyluridine (Pro. Bio. Sint., Varese,  
25 Italy, 100.0g, 0.416 mmol), dimethylaminopyridine (0.66g, 0.013eq, 0.0054mmol) were dissolved in dry pyridine (500 ml) at ambient temperature under an argon atmosphere and with mechanical stirring. tert-Butyldiphenylchlorosilane (125.8g, 119.0mL, 1.1eq, 0.458mmol) was added in one portion. The  
30 reaction was stirred for 16 h at ambient temperature. TLC ( $R_f$  0.22, EtOAc) indicated a complete reaction. The solution was concentrated under reduced pressure to a thick oil. This was partitioned between  $\text{CH}_2\text{Cl}_2$  (1 L) and saturated sodium bicarbonate (2 x 1 L) and brine (1 L). The organic layer was  
35 dried over sodium sulfate, filtered, and concentrated under reduced pressure to a thick oil. The oil was dissolved in a 1:1 mixture of EtOAc and ethyl ether (600mL) and cooling the



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solution to -10°C afforded a white crystalline solid which was collected by filtration, washed with ethyl ether (3 x 200 mL) and dried (40°C, 1mm Hg, 24 h) to afford 149g of white solid (74.8%). TLC and NMR spectroscopy were consistent with pure product.

**5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine**

In the fume hood, ethylene glycol (350 mL, excess) was added cautiously with manual stirring to a 2 L stainless steel pressure reactor containing borane in tetrahydrofuran (1.0 M, 2.0 eq, 622 mL). (Caution : evolves hydrogen gas). 5'-O-tert-Butyldiphenylsilyl-0<sup>2</sup>-2'-anhydro-5-methyluridine (149 g, 0.311 mol) and sodium bicarbonate (0.074 g, 0.003 eq) were added with manual stirring. The reactor was sealed and heated in an oil bath until an internal temperature of 160 °C was reached and then maintained for 16 h (pressure < 100 psig). The reaction vessel was cooled to ambient temperature and opened. TLC (EtOAc, R<sub>f</sub> 0.67 for desired product and R<sub>f</sub> 0.82 for ara-T side product) indicated about 70% conversion to the product. The solution was concentrated under reduced pressure (10 to 1mm Hg) in a warm water bath (40-100°C) with the more extreme conditions used to remove the ethylene glycol. (Alternatively, once the THF has evaporated the solution can be diluted with water and the product extracted into EtOAc). The residue was purified by column chromatography (2kg silica gel, EtOAc-hexanes gradient 1:1 to 4:1). The appropriate fractions were combined, evaporated and dried to afford 84 g of a white crisp foam (50%), contaminated starting material (17.4g, 12% recovery) and pure reusable starting material (20g, 13% recovery). TLC and NMR spectroscopy were consistent with 99% pure product.

**2'-O-([2-phthalimidoxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine**

5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine (20g, 36.98mmol) was mixed with

triphenylphosphine (11.63g, 44.36mmol) and N-hydroxyphthalimide (7.24g, 44.36mmol) and dried over  $P_2O_5$  under high vacuum for two days at 40°C. The reaction mixture was flushed with argon and dissolved in dry THF (369.8mL, Aldrich, sure seal bottle). Diethyl-azodicarboxylate (6.98mL, 44.36mmol) was added dropwise to the reaction mixture with the rate of addition maintained such that the resulting deep red coloration is just discharged before adding the next drop. The reaction mixture was stirred for 4 hrs., after which time TLC (EtOAc:hexane, 60:40) indicated that the reaction was complete. The solvent was evaporated in vacuo and the residue purified by flash column chromatography (eluted with 60:40 EtOAc:hexane), to yield 2'-O-([2-phthalimidooxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine as white foam (21.819 g, 86%) upon rotary evaporation.

**5'-O-tert-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy)ethyl]-5-methyluridine**

2'-O-([2-phthalimidooxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine (3.1g, 4.5mmol) was dissolved in dry  $CH_2Cl_2$  (4.5mL) and methylhydrazine (300mL, 4.64mmol) was added dropwise at -10°C to 0°C. After 1 h the mixture was filtered, the filtrate washed with ice cold  $CH_2Cl_2$ , and the combined organic phase was washed with water and brine and dried (anhydrous  $Na_2SO_4$ ). The solution was filtered and evaporated to afford 2'-O-(aminooxyethyl) thymidine, which was then dissolved in MeOH (67.5mL). Formaldehyde (20% aqueous solution, w/w, 1.1 eq.) was added and the resulting mixture was stirred for 1 h. The solvent was removed under vacuum and the residue was purified by column chromatography to yield 5'-O-tert-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy)ethyl]-5-methyluridine as white foam (1.95 g, 78%) upon rotary evaporation.

**5'-O-tert-Butyldiphenylsilyl-2'-O-[N,N dimethylaminooxyethyl]-5-methyluridine**

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5'-O-*tert*-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy)ethyl]-5-methyluridine (1.77g, 3.12mmol) was dissolved in a solution of 1M pyridinium *p*-toluenesulfonate (PPTS) in dry MeOH (30.6mL) and cooled to 10°C under inert atmosphere. Sodium cyanoborohydride (0.39g, 6.13mmol) was added and the reaction mixture was stirred. After 10 minutes the reaction was warmed to room temperature and stirred for 2 h. while the progress of the reaction was monitored by TLC (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>). Aqueous NaHCO<sub>3</sub> solution (5%, 10mL) was added and the product was extracted with EtOAc (2 x 20 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to dryness. This entire procedure was repeated with the resulting residue, with the exception that formaldehyde (20% w/w, 30 mL, 3.37 mol) was added upon dissolution of the residue in the PPTS/MeOH solution. After the extraction and evaporation, the residue was purified by flash column chromatography and (eluted with 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 5'-O-*tert*-butyldiphenylsilyl-2'-O-[N,N-dimethylaminooxyethyl]-5-methyluridine as a white foam (14.6g, 80%) upon rotary evaporation.

**2'-O-(dimethylaminooxyethyl)-5-methyluridine**

Triethylamine trihydrofluoride (3.91mL, 24.0mmol) was dissolved in dry THF and TEA (1.67mL, 12mmol, dry, stored over KOH) and added to 5'-O-*tert*-butyldiphenylsilyl-2'-O-[N,N-dimethylaminooxyethyl]-5-methyluridine (1.40g, 2.4mmol). The reaction was stirred at room temperature for 24 hrs and monitored by TLC (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>). The solvent was removed under vacuum and the residue purified by flash column chromatography (eluted with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 2'-O-(dimethylaminooxyethyl)-5-methyluridine (766mg, 92.5%) upon rotary evaporation of the solvent.

**5'-O-DMT-2'-O-(dimethylaminooxyethyl)-5-methyluridine**

2'-O-(dimethylaminooxyethyl)-5-methyluridine (750 mg, 2.17 mmol) was dried over P<sub>2</sub>O<sub>5</sub> under high vacuum overnight at 40°C, co-evaporated with anhydrous pyridine (20 mL), and

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dissolved in pyridine (11 mL) under argon atmosphere. 4-dimethylaminopyridine (26.5 mg, 2.60 mmol) and 4,4'-dimethoxytrityl chloride (880 mg, 2.60 mmol) were added to the pyridine solution and the reaction mixture was stirred at room temperature until all of the starting material had reacted. Pyridine was removed under vacuum and the residue was purified by column chromatography (eluted with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> containing a few drops of pyridine) to yield 5'-O-DMT-2'-O-(dimethylamino-oxyethyl)-5-methyluridine (1.13g, 80%) upon rotary evaporation.

**5'-O-DMT-2'-O-(2-N,N-dimethylaminooxyethyl)-5-methyluridine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite]**

5'-O-DMT-2'-O-(dimethylaminooxyethyl)-5-methyluridine (1.08 g, 1.67 mmol) was co-evaporated with toluene (20 mL), N,N-diisopropylamine tetrazonide (0.29 g, 1.67 mmol) was added and the mixture was dried over P<sub>2</sub>O<sub>5</sub> under high vacuum overnight at 40°C. This was dissolved in anhydrous acetonitrile (8.4 mL) and 2-cyanoethyl-N,N,N',N'-tetraisopropylphosphoramidite (2.12 mL, 6.08 mmol) was added. The reaction mixture was stirred at ambient temperature for 4 h under inert atmosphere. The progress of the reaction was monitored by TLC (hexane:EtOAc 1:1). The solvent was evaporated, then the residue was dissolved in EtOAc (70mL) and washed with 5% aqueous NaHCO<sub>3</sub> (40mL). The EtOAc layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue obtained was purified by column chromatography (EtOAc as eluent) to afford 5'-O-DMT-2'-O-(2-N,N-dimethylaminooxyethyl)-5-methyluridine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite] as a foam (1.04g, 74.9%) upon rotary evaporation.

**2'-(Aminooxyethoxy) nucleoside amidites**

2'-(Aminooxyethoxy) nucleoside amidites (also known in the art as 2'-O-(aminooxyethyl) nucleoside amidites) are prepared as described in the following paragraphs. Adenosine,

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cytidine and thymidine nucleoside amidites are prepared similarly.

5        **N2-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite]**

The 2'-O-aminooxyethyl guanosine analog may be obtained by selective 2'-O-alkylation of diaminopurine riboside. Multigram quantities of diaminopurine riboside may be  
10        purchased from Schering AG (Berlin) to provide 2'-O-(2-ethylacetyl) diaminopurine riboside along with a minor amount of the 3'-O-isomer. 2'-O-(2-ethylacetyl) diaminopurine riboside may be resolved and converted to 2'-O-(2-ethylacetyl)guanosine by treatment with adenosine deaminase.  
15        (McGee, D. P. C., Cook, P. D., Guinasso, C. J., WO 94/02501 A1 940203.) Standard protection procedures should afford 2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine and 2-N-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine which may be reduced to  
20        provide 2-N-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-hydroxyethyl)-5'-O-(4,4'-dimethoxytrityl)guanosine. As before the hydroxyl group may be displaced by N-hydroxyphthalimide via a Mitsunobu reaction, and the protected nucleoside may be phosphitylated as usual to yield 2-N-isobutyryl-6-O-  
25        diphenylcarbamoyl-2'-O-([2-phthalamidoxy]ethyl)-5'-O-(4,4'-dimethoxytrityl)guanosine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite].

**2'-dimethylaminoethoxyethoxy (2'-DMAEOE) nucleoside amidites**  
30        2'-dimethylaminoethoxyethoxy nucleoside amidites (also known in the art as 2'-O-dimethylaminoethoxyethyl, i.e., 2'-O-CH<sub>2</sub>-O-CH<sub>2</sub>-N(CH<sub>2</sub>)<sub>2</sub>, or 2'-DMAEOE nucleoside amidites) are prepared as follows. Other nucleoside amidites are prepared similarly.

35

**2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl]-5-methyl uridine**

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2[2-(Dimethylamino)ethoxy]ethanol (Aldrich, 6.66 g, 50 mmol) was slowly added to a solution of borane in tetrahydrofuran (1 M, 10 mL, 10 mmol) with stirring in a 100 mL bomb. (Caution: Hydrogen gas evolves as the solid  
5 dissolves). 0<sup>2</sup>-,2'-anhydro-5-methyluridine (1.2 g, 5 mmol), and sodium bicarbonate (2.5 mg) were added and the bomb was sealed, placed in an oil bath and heated to 155°C for 26 h. then cooled to room temperature. The crude solution was concentrated, the residue was diluted with water (200 mL) and  
10 extracted with hexanes (200 mL). The product was extracted from the aqueous layer with EtOAc (3 x 200 mL) and the combined organic layers were washed once with water, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography  
15 (eluted with 5:100:2 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/TEA) as the eluent. The appropriate fractions were combined and evaporated to afford the product as a white solid.

20 **5'-O-dimethoxytrityl-2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl]-5-methyl uridine**

To 0.5 g (1.3 mmol) of 2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl]-5-methyl uridine in anhydrous pyridine (8 mL), was added TEA (0.36 mL) and dimethoxytrityl chloride (DMT-Cl, 0.87 g, 2 eq.) and the reaction was stirred for 1 h. The  
25 reaction mixture was poured into water (200 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 200 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> layers were washed with saturated NaHCO<sub>3</sub> solution, followed by saturated NaCl solution, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel  
30 column chromatography (eluted with 5:100:1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/TEA) to afford the product.

35 **5'-O-Dimethoxytrityl-2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl]-5-methyl uridine-3'-O-(cyanoethyl-N,N-diisopropyl)phosphoramidite**

Diisopropylaminotetrazolide (0.6 g) and 2-cyanoethoxy-N,N-diisopropyl phosphoramidite (1.1 mL, 2 eq.) were added to

Alkylphosphonothioate oligonucleotides are prepared as

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described in published PCT applications PCT/US94/00902 and PCT/US93/06976 (published as WO 94/17093 and WO 94/02499, respectively), herein incorporated by reference.

3'-Deoxy-3'-amino phosphoramidate oligonucleotides are prepared as described in U.S. Patent 5,476,925, herein incorporated by reference.

Phosphotriester oligonucleotides are prepared as described in U.S. Patent 5,023,243, herein incorporated by reference.

Borano phosphate oligonucleotides are prepared as described in U.S. Patents 5,130,302 and 5,177,198, both herein incorporated by reference.

### Example 3

#### 15 Oligonucleoside Synthesis

Methylenemethylimino linked oligonucleosides, also identified as MMI linked oligonucleosides, methylenedimethylhydrazo linked oligonucleosides, also identified as MDH linked oligonucleosides, and methylenecarbonylamino linked oligonucleosides, also identified as amide-3 linked oligonucleosides, and methyleneaminocarbonyl linked oligonucleosides, also identified as amide-4 linked oligonucleosides, as well as mixed backbone compounds having, for instance, alternating MMI and P=O or P=S linkages are prepared as described in U.S. Patents 5,378,825, 5,386,023, 5,489,677, 5,602,240 and 5,610,289, all of which are herein incorporated by reference.

Formacetal and thioformacetal linked oligonucleosides are prepared as described in U.S. Patents 5,264,562 and 5,264,564, herein incorporated by reference.

Ethylene oxide linked oligonucleosides are prepared as described in U.S. Patent 5,223,618, herein incorporated by reference.

#### 35 Example 4

#### PNA Synthesis

Peptide nucleic acids (PNAs) are prepared in accordance



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with any of the various procedures referred to in Peptide Nucleic Acids (PNA): Synthesis, Properties and Potential Applications, *Bioorganic & Medicinal Chemistry*, 1996, 4, 5-23. They may also be prepared in accordance with U.S.

5 Patents 5,539,082, 5,700,922, and 5,719,262, herein incorporated by reference.

#### Example 5

#### Synthesis of Chimeric Oligonucleotides

10 Chimeric oligonucleotides, oligonucleosides or mixed oligonucleotides/oligonucleosides of the invention can be of several different types. These include a first type wherein the "gap" segment of linked nucleosides is positioned between 5' and 3' "wing" segments of linked nucleosides and a second  
15 "open end" type wherein the "gap" segment is located at either the 3' or the 5' terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as "gapmers" or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as "hemimers" or  
20 "wingmers".

#### [2'-O-Me]--[2'-deoxy]--[2'-O-Me] Chimeric Phosphorothioate Oligonucleotides

Chimeric oligonucleotides having 2'-O-alkyl phosphorothioate and 2'-deoxy phosphorothioate oligo-  
25 nucleotide segments are synthesized using an Applied Biosystems automated DNA synthesizer Model 394, as above. Oligonucleotides are synthesized using the automated synthesizer and 2'-deoxy-5'-dimethoxytrityl-3'-O-phosphoramidite for the DNA portion and 5'-dimethoxytrityl-2'-O-methyl-3'-O-phosphoramidite for 5' and 3' wings. The  
30 standard synthesis cycle is modified by incorporating coupling steps with increased reaction times for the 5'-dimethoxytrityl-2'-O-methyl-3'-O-phosphoramidite. The fully protected oligonucleotide is cleaved from the support and  
35 deprotected in concentrated ammonia (NH<sub>4</sub>OH) for 12-16 hr at 55°C. The deprotected oligo is then recovered by an appropriate method (precipitation, column chromatography,

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volume reduced in vacuo and analyzed spectrophotometrically for yield and for purity by capillary electrophoresis and by mass spectrometry.

5        [2'-O-(2-Methoxyethyl)]--[2'-deoxy]--[2'-O-(Methoxyethyl)] Chimeric Phosphorothioate Oligonucleotides  
       [2'-O-(2-methoxyethyl)]--[2'-deoxy]--[2'-O-(methoxyethyl)] chimeric phosphorothioate oligonucleotides  
 10       were prepared as per the procedure above for the 2'-O-methyl chimeric oligonucleotide, with the substitution of 2'-O-(methoxyethyl) amidites for the 2'-O-methyl amidites.

15       [2'-O-(2-Methoxyethyl)Phosphodiester]--[2'-deoxy Phosphorothioate]--[2'-O-(2-Methoxyethyl) Phosphodiester] Chimeric Oligonucleotides  
       [2'-O-(2-methoxyethyl phosphodiester)]--[2'-deoxy phosphorothioate]--[2'-O-(methoxyethyl) phosphodiester] chimeric oligonucleotides are prepared as per the above  
 20       procedure for the 2'-O-methyl chimeric oligonucleotide with the substitution of 2'-O-(methoxyethyl) amidites for the 2'-O-methyl amidites, oxidation with iodine to generate the phosphodiester internucleotide linkages within the wing portions of the chimeric structures and sulfurization  
 25       utilizing 3,4-benzodithiole-3-one 1,1 dioxide (Beaucage Reagent) to generate the phosphorothioate internucleotide linkages for the center gap.

      Other chimeric oligonucleotides, chimeric oligonucleosides and mixed chimeric  
 30       oligonucleotides/oligonucleosides are synthesized according to United States patent 5,623,065, herein incorporated by reference.

#### Example 6

#### 35       Oligonucleotide Isolation

      After cleavage from the controlled pore glass solid support and deblocking in concentrated ammonium hydroxide at

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55°C for 12-16 hours, the oligonucleotides or oligonucleosides are recovered by precipitation out of 1 M  $\text{NH}_4\text{OAc}$  with >3 volumes of ethanol. Synthesized oligonucleotides were analyzed by electrospray mass spectroscopy (molecular weight determination) and by capillary gel electrophoresis and judged to be at least 70% full length material. The relative amounts of phosphorothioate and phosphodiester linkages obtained in the synthesis was determined by the ratio of correct molecular weight relative to the -16 amu product (+/- 32 +/-48). For some studies oligonucleotides were purified by HPLC, as described by Chiang et al., *J. Biol. Chem.* **1991**, 266, 18162-18171. Results obtained with HPLC-purified material were similar to those obtained with non-HPLC purified material.

15

**Example 7****Oligonucleotide Synthesis - 96 Well Plate Format**

Oligonucleotides were synthesized via solid phase P(III) phosphoramidite chemistry on an automated synthesizer capable of assembling 96 sequences simultaneously in a 96-well format. Phosphodiester internucleotide linkages were afforded by oxidation with aqueous iodine. Phosphorothioate internucleotide linkages were generated by sulfurization utilizing 3,4-dihydro-2H-benzodithiole-3-one 1,1 dioxide (Beaucage Reagent) in anhydrous acetonitrile. Standard base-protected beta-cyanoethyl-diisopropyl phosphoramidites were purchased from commercial vendors (e.g. PE-Applied Biosystems, Foster City, CA, or Pharmacia, Piscataway, NJ). Non-standard nucleosides are synthesized as per standard or patented methods. They are utilized as base protected beta-cyanoethyldiisopropyl phosphoramidites.

Oligonucleotides were cleaved from support and deprotected with concentrated  $\text{NH}_4\text{OH}$  at elevated temperature (55-60°C) for 12-16 hours and the released product then dried in vacuo. The dried product was then re-suspended in sterile water to afford a master plate from which all analytical and

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test plate samples are then diluted utilizing robotic pipettors.

**Example 8****5 Oligonucleotide Analysis - 96-Well Plate Format**

The concentration of oligonucleotide in each well was assessed by dilution of samples and UV absorption spectroscopy. The full-length integrity of the individual products was evaluated by capillary electrophoresis (CE) in  
10 either the 96-well format (Beckman P/ACE™ MDQ) or, for individually prepared samples, on a commercial CE apparatus (e.g., Beckman P/ACE™ 5000, ABI 270). Base and backbone composition was confirmed by mass analysis of the compounds utilizing electrospray-mass spectroscopy. All assay test  
15 plates were diluted from the master plate using single and multi-channel robotic pipettors. Plates were judged to be acceptable if at least 85% of the compounds on the plate were at least 85% full length.

**20 Example 9****Cell culture and oligonucleotide treatment**

The effect of antisense compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the target nucleic acid is present at  
25 measurable levels. This can be routinely determined using, for example, PCR or Northern blot analysis. The following cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen. This can be readily  
30 determined by methods routine in the art, for example Northern blot analysis, ribonuclease protection assays, or RT-PCR.

**T-24 cells:**

35 The human transitional cell bladder carcinoma cell line T-24 was obtained from the American Type Culture Collection (ATCC) (Manassas, VA). T-24 cells were routinely cultured in

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complete McCoy's 5A basal media (Invitrogen Corporation, Carlsbad, CA) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, CA), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, CA). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 7000 cells/well for use in RT-PCR analysis.

For Northern blotting or other analysis, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

#### A549 cells:

The human lung carcinoma cell line A549 was obtained from the American Type Culture Collection (ATCC) (Manassas, VA). A549 cells were routinely cultured in DMEM basal media (Invitrogen Corporation, Carlsbad, CA) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, CA), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, CA). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence.

#### NHDF cells:

Human neonatal dermal fibroblast (NHDF) were obtained from the Clonetics Corporation (Walkersville, MD). NHDFs were routinely maintained in Fibroblast Growth Medium (Clonetics Corporation, Walkersville, MD) supplemented as recommended by the supplier. Cells were maintained for up to 10 passages as recommended by the supplier.

#### HEK cells:

Human embryonic keratinocytes (HEK) were obtained from the Clonetics Corporation (Walkersville, MD). HEKs were routinely maintained in Keratinocyte Growth Medium (Clonetics Corporation, Walkersville, MD) formulated as recommended by

The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control oligonucleotide is selected from either ISIS 13920 (TCCGTCATCGCTCCTCAGGG, SEQ ID NO: 1) which is targeted to human H-ras, or ISIS 18078, (GTGCGCGCGAGCCCGAAATC, SEQ ID NO: 2) which is targeted to human Jun-N-terminal kinase-2 (JNK2). Both controls are 2'-O-methoxyethyl gapmers (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone. For mouse or rat cells the positive control oligonucleotide is ISIS 15770, ATGCATTCTGCCCCCAAGGA, SEQ ID NO: 3, a 2'-O-methoxyethyl gapmer (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to both mouse and rat c-raf. The concentration of positive control oligonucleotide that results in 80% inhibition of c-Ha-ras (for ISIS 13920) or c-raf (for ISIS 15770) mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of H-ras or c-raf mRNA is then utilized as the oligonucleotide screening concentration in

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subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments.

5 **Example 10**

**Analysis of oligonucleotide inhibition of SMRT expression**

Antisense modulation of SMRT expression can be assayed in a variety of ways known in the art. For example, SMRT mRNA levels can be quantitated by, e.g., Northern blot  
 10 analysis, competitive polymerase chain reaction (PCR), or real-time PCR (RT-PCR). Real-time quantitative PCR is presently preferred. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. The preferred method of RNA  
 15 analysis of the present invention is the use of total cellular RNA as described in other examples herein. Methods of RNA isolation are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.1.1-4.2.9 and 4.5.1-4.5.3, John Wiley & Sons, Inc., 1993. Northern blot analysis is routine in the art and is taught  
 20 in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.2.1-4.2.9, John Wiley & Sons, Inc., 1996. Real-time quantitative (PCR) can be conveniently accomplished using the commercially available ABI PRISM™ 7700 Sequence Detection System, available from PE-  
 25 Applied Biosystems, Foster City, CA and used according to manufacturer's instructions.

Protein levels of SMRT can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), ELISA or  
 30 fluorescence-activated cell sorting (FACS). Antibodies directed to SMRT can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional antibody generation methods. Methods for  
 35 preparation of polyclonal antisera are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.12.1-11.12.9, John Wiley

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& Sons, Inc., 1997). Preparation of monoclonal antibodies is taught in, for example, Ausubel, F.M. et al., (*Current Protocols in Molecular Biology*, Volume 2, pp. 11.4.1-11.11.5, John Wiley & Sons, Inc., 1997).

5 Immunoprecipitation methods are standard in the art and can be found at, for example, Ausubel, F.M. et al., (*Current Protocols in Molecular Biology*, Volume 2, pp. 10.16.1-10.16.11, John Wiley & Sons, Inc., 1998). Western blot (immunoblot) analysis is standard in the art and can be found  
10 at, for example, Ausubel, F.M. et al., (*Current Protocols in Molecular Biology*, Volume 2, pp. 10.8.1-10.8.21, John Wiley & Sons, Inc., 1997). Enzyme-linked immunosorbent assays (ELISA) are standard in the art and can be found at, for  
15 example, Ausubel, F.M. et al., (*Current Protocols in Molecular Biology*, Volume 2, pp. 11.2.1-11.2.22, John Wiley & Sons, Inc., 1991).

#### Example 11

##### Poly(A)+ mRNA isolation

20 Poly(A)+ mRNA was isolated according to Miura et al., (*Clin. Chem.*, 1996, 42, 1758-1764). Other methods for poly(A)+ mRNA isolation are taught in, for example, Ausubel, F.M. et al., (*Current Protocols in Molecular Biology*, Volume 1, pp. 4.5.1-4.5.3, John Wiley & Sons, Inc., 1993). Briefly,  
25 for cells grown on 96-well plates, growth medium was removed from the cells and each well was washed with 200  $\mu$ L cold PBS. 60  $\mu$ L lysis buffer (10 mM Tris-HCl, pH 7.6, 1 mM EDTA, 0.5 M NaCl, 0.5% NP-40, 20 mM vanadyl-ribonucleoside complex) was added to each well, the plate was gently agitated and then  
30 incubated at room temperature for five minutes. 55  $\mu$ L of lysate was transferred to Oligo d(T) coated 96-well plates (AGCT Inc., Irvine CA). Plates were incubated for 60 minutes at room temperature, washed 3 times with 200  $\mu$ L of wash  
buffer (10 mM Tris-HCl pH 7.6, 1 mM EDTA, 0.3 M NaCl). After  
35 the final wash, the plate was blotted on paper towels to remove excess wash buffer and then air-dried for 5 minutes.



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60  $\mu$ L of elution buffer (5 mM Tris-HCl pH 7.6), preheated to 70°C, was added to each well, the plate was incubated on a 90°C hot plate for 5 minutes, and the eluate was then transferred to a fresh 96-well plate.

- 5 Cells grown on 100 mm or other standard plates may be treated similarly, using appropriate volumes of all solutions.

#### Example 12

#### 10 Total RNA Isolation

- Total RNA was isolated using an RNEASY 96™ kit and buffers purchased from Qiagen Inc. (Valencia, CA) following the manufacturer's recommended procedures. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well was washed with 200  $\mu$ L cold PBS. 150  $\mu$ L Buffer RLT was added to each well and the plate vigorously agitated for 20 seconds. 150  $\mu$ L of 70% ethanol was then added to each well and the contents mixed by pipetting three times up and down. The samples were then transferred to the RNEASY 96™ well plate attached to a QIAVAC™ manifold fitted with a waste collection tray and attached to a vacuum source. Vacuum was applied for 1 minute. 500  $\mu$ L of Buffer RW1 was added to each well of the RNEASY 96™ plate and incubated for 15 minutes and the vacuum was again applied for 1 minute. An additional 500  $\mu$ L of Buffer RW1 was added to each well of the RNEASY 96™ plate and the vacuum was applied for 2 minutes. 1 mL of Buffer RPE was then added to each well of the RNEASY 96™ plate and the vacuum applied for a period of 90 seconds. The Buffer RPE wash was then repeated and the vacuum was applied for an additional 3 minutes. The plate was then removed from the QIAVAC™ manifold and blotted dry on paper towels. The plate was then re-attached to the QIAVAC™ manifold fitted with a collection tube rack containing 1.2 mL collection tubes. RNA was then eluted by pipetting 170  $\mu$ L

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water into each well, incubating 1 minute, and then applying the vacuum for 3 minutes.

The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia CA). Essentially, after lysing of the cells on the culture plate, the plate is transferred to the robot deck where the pipetting, DNase treatment and elution steps are carried out.

10

**Example 13****Real-time Quantitative PCR Analysis of SMRT mRNA Levels**

Quantitation of SMRT mRNA levels was determined by real-time quantitative PCR using the ABI PRISM™ 7700 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. This is a closed-tube, non-gel-based, fluorescence detection system which allows high-throughput quantitation of polymerase chain reaction (PCR) products in real-time. As opposed to standard PCR in which amplification products are quantitated after the PCR is completed, products in real-time quantitative PCR are quantitated as they accumulate. This is accomplished by including in the PCR reaction an oligonucleotide probe that anneals specifically between the forward and reverse PCR primers, and contains two fluorescent dyes. A reporter dye (e.g., FAM or JOE, obtained from either PE-Applied Biosystems, Foster City, CA, Operon Technologies Inc., Alameda, CA or Integrated DNA Technologies Inc., Coralville, IA) is attached to the 5' end of the probe and a quencher dye (e.g., TAMRA, obtained from either PE-Applied Biosystems, Foster City, CA, Operon Technologies Inc., Alameda, CA or Integrated DNA Technologies Inc., Coralville, IA) is attached to the 3' end of the probe. When the probe and dyes are intact, reporter dye emission is quenched by the proximity of the 3' quencher dye. During amplification, annealing of the probe to the target sequence creates a substrate that can be cleaved by the 5'-exonuclease activity of Taq polymerase.

PCR reagents were obtained from Invitrogen Corporation, (Carlsbad, CA). RT-PCR reactions were carried out by adding 20  $\mu$ L PCR cocktail (2.5x PCR buffer (-MgCl<sub>2</sub>), 6.6 mM MgCl<sub>2</sub>, 375  $\mu$ M each of dATP, dCTP, dGTP and dTTP, 375 nM each of forward primer and reverse primer, 125 nM of probe, 4 Units RNase inhibitor, 1.25 Units PLATINUM® Taq, 5 Units MuLV

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reverse transcriptase, and 2.5x ROX dye) to 96-well plates containing 30  $\mu$ L total RNA solution. The RT reaction was carried out by incubation for 30 minutes at 48°C. Following a 10 minute incubation at 95°C to activate the PLATINUM® Taq, 40  
5 cycles of a two-step PCR protocol were carried out: 95°C for 15 seconds (denaturation) followed by 60°C for 1.5 minutes (annealing/extension).

Gene target quantities obtained by real time RT-PCR are normalized using either the expression level of GAPDH, a gene  
10 whose expression is constant, or by quantifying total RNA using RiboGreen™ (Molecular Probes, Inc. Eugene, OR). GAPDH expression is quantified by real time RT-PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RiboGreen™ RNA quantification  
15 reagent from Molecular Probes. Methods of RNA quantification by RiboGreen™ are taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374).

In this assay, 170  $\mu$ L of RiboGreen™ working reagent (RiboGreen™ reagent diluted 1:350 in 10mM Tris-HCl, 1 mM  
20 EDTA, pH 7.5) is pipetted into a 96-well plate containing 30  $\mu$ L purified, cellular RNA. The plate is read in a CytoFluor 4000 (PE Applied Biosystems) with excitation at 480nm and emission at 520nm.

Probes and primers to human SMRT were designed to  
25 hybridize to a human SMRT sequence, using published sequence information (GenBank accession number AF125672.1, incorporated herein as SEQ ID NO:4). For human SMRT the PCR primers were:

forward primer: CACACATCGTTGCCGCAG (SEQ ID NO: 5)  
30 reverse primer: AAGGTATCAAAAATATACCCTGTAAACCA (SEQ ID NO: 6)  
and the PCR probe was: FAM-TGGGAAGGAAAGGCAGATGTAAATGATGTG-TAMRA

(SEQ ID NO: 7) where FAM is the fluorescent dye and TAMRA is the quencher dye. For human GAPDH the PCR primers were:

35 forward primer: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:8)  
reverse primer: GAAGATGGTGATGGGATTTTC (SEQ ID NO:9) and the

PCR probe was: 5' JOE-CAAGCTTCCCGTTCTCAGCC-TAMRA 3' (SEQ ID NO: 10) where JOE is the fluorescent reporter dye and TAMRA is the quencher dye.

5

### Example 14

### Northern blot analysis of SMRT mRNA levels

Eighteen hours after antisense treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL™ (TEL-TEST "B" Inc., Friendswood, TX). Total RNA was prepared following manufacturer's recommended protocols. Twenty micrograms of total RNA was fractionated by electrophoresis through 1.2% agarose gels containing 1.1% formaldehyde using a MOPS buffer system (AMRESCO, Inc. Solon, OH). RNA was transferred from the gel to HYBOND™-N+ nylon membranes (Amersham Pharmacia Biotech, Piscataway, NJ) by overnight capillary transfer using a Northern/Southern Transfer buffer system (TEL-TEST "B" Inc., Friendswood, TX). RNA transfer was confirmed by UV visualization. Membranes were fixed by UV cross-linking using a STRATALINKER™ UV Crosslinker 2400 (Stratagene, Inc, La Jolla, CA) and then probed using QUICKHYB™ hybridization solution (Stratagene, La Jolla, CA) using manufacturer's recommendations for stringent conditions.

25 To detect human SMRT, a human SMRT specific probe was prepared by PCR using the forward primer CACACATCGTTGCCGCAG (SEQ ID NO: 5) and the reverse primer AAGGTATCAAAAATATACCCTGTAAACCA (SEQ ID NO: 6). To normalize for variations in loading and transfer efficiency membranes  
30 were stripped and probed for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, CA).

Hybridized membranes were visualized and quantitated using a PHOSPHORIMAGER™ and IMAGEQUANT™ Software V3.3 (Molecular Dynamics, Sunnyvale, CA). Data was normalized to GAPDH levels in untreated controls.

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**Example 15****Antisense inhibition of human SMRT expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap**

5 In accordance with the present invention, a series of oligonucleotides were designed to target different regions of the human SMRT RNA, using published sequences (GenBank accession number AF125672.1, incorporated herein as SEQ ID NO: 4; GenBank accession number NM\_006312.1, incorporated  
10 herein as SEQ ID NO: 11; the complement of residues 39001-260000 of GenBank accession number NT\_009459.3, representing a partial genomic sequence of SMRT, incorporated herein as SEQ ID NO: 12; and GenBank accession number S83390.1, incorporated herein as SEQ ID NO: 13). The oligonucleotides  
15 are shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 1 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten  
20 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues  
25 are 5-methylcytidines. The compounds were analyzed for their effect on human SMRT mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments in which A549 cells were treated with the antisense oligonucleotides of the present invention. The  
30 positive control for each datapoint is identified in the table by sequence ID number. If present, "N.D." indicates "no data".

Table 1

35 Inhibition of human SMRT mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

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ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
121624	5'UTR	4	61	agtcctcgtcatcagctcac	13	14	2
152703	Coding	11	2705	ctcttggcagtggtggccct	63	15	2
152708	Coding	11	6987	atgttcctgcaccgcctggc	82	16	2
195343	5'UTR	4	10	ctccagcgaggctgtgtcct	77	17	2
195344	5'UTR	4	30	tcactggcaccagaaactgc	32	18	2
195345	Start Codon	4	150	tggagccccgacatggtggtg	27	19	2
195346	Coding	4	635	cctggcgccgaccagctcca	63	20	2
195347	Coding	4	1203	gctggcccaccctctgcatg	70	21	2
195348	Coding	4	1856	gctgttggcagttttgcggc	21	22	2
195349	Coding	4	2311	ttgacagtggcttcagcctc	24	23	2
195350	Coding	4	3194	aggcttctctgcctccttgt	49	24	2
195351	Coding	4	3752	tgtgctgggaatgcctttgg	75	25	2
195352	Coding	4	5930	ctccttgggcagcaagacgg	73	26	2
195353	Coding	4	7307	gccgccacctggcgaggtga	52	27	2
195354	Stop Codon	4	7670	tgttctgagtcactcgctgt	57	28	2
195355	3'UTR	4	8323	catcatttacatctgccttt	39	29	2
195356	Coding	11	1048	ggcccaccctgctctgcatg	69	30	2
195357	Coding	11	2159	gcatgtaaggcttcagcctc	0	31	2
195358	Coding	11	2172	ctcattcccagaggcatgta	76	32	2
195359	Coding	11	2210	ttgacagtggctggccact	38	33	2
195360	Coding	11	3092	gctgcgaaggcctccttgtc	48	34	2
195361	Exon: Intron Junction	12	926	atgaacctaccagaaactgc	33	35	2
195362	Intron	12	5600	accagacaaggctctgggct	38	36	2
195363	Intron: Exon Junction	12	41188	tcactggcacctgcgggaaa	30	37	2
195364	Exon: Intron Junction	12	41410	accccccttaccgtgtgcgtc	31	38	2
195365	Intron	12	72430	cccagtgtcctgaattccta	51	39	2
195366	Intron: Exon Junction	12	82830	cagccttcttctgcagggtg	34	40	2
195367	Intron: Exon Junction	12	110566	cgctggccccaccctgctggg	48	41	2
195368	Intron	12	121997	gaccgagttcagccccaggc	30	42	2
195369	Intron: Exon Junction	12	166452	gcatgtaaggctggaaggaa	68	43	2
195370	Exon: Intron Junction	12	166503	acattcgctacctgggccact	66	44	2
195371	Intron: Exon Junction	12	184109	ggcttctctgctgagggcag	69	45	2
195372	Intron: Exon Junction	12	184133	gctgcgaaggctgggaagaa	68	46	2

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195373	Intron	12	195790	cacttggttacttactgccct	63	47	2
195374	Exon: Intron Junction	12	217191	tcatattttacccatgagtg	63	48	2
195375	Exon: Intron Junction	12	217330	ggcctgcagacctggcgagg	62	49	2
195376	Coding	13	2392	gccgccacccatgagtgct	72	50	2

As shown in Table 1, SEQ ID NOS 15, 16, 17, 20, 21, 24, 25, 26, 27, 28, 30, 32, 34, 39, 41, 43, 44, 45, 46, 47, 48, 49 and 50 demonstrated at least 40% inhibition of human SMRT expression in this assay and are therefore preferred. The target sites to which these preferred sequences are complementary are herein referred to as "preferred target regions" and are therefore preferred sites for targeting by compounds of the present invention. These preferred target regions are shown in Table 2. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number of the corresponding target nucleic acid. Also shown in Table 2 is the species in which each of the preferred target regions was found.

20

Table 2

Sequence and position of preferred target regions identified in SMRT.

SITEID	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	REV COMP OF SEQ ID	ACTIVE IN	SEQ ID NO
68267	11	2705	agggccaccactgccaagag	15	<i>H. sapiens</i>	51
68272	11	6987	gccaggcgggtgcaggaacat	16	<i>H. sapiens</i>	52
113455	4	10	aggacacagcctcgctggag	17	<i>H. sapiens</i>	53
113458	4	635	tggagctggtgcccgcacgg	20	<i>H. sapiens</i>	54
113459	4	1203	catgcagaggggtgggccagc	21	<i>H. sapiens</i>	55
113462	4	3194	acaaggaggcagagaagcct	24	<i>H. sapiens</i>	56
113463	4	3752	caaaggcattcccagcaca	25	<i>H. sapiens</i>	57
113464	4	5930	ccgtcttgctgccaaggag	26	<i>H. sapiens</i>	58
113465	4	7307	tcacctcgccaggtggcggc	27	<i>H. sapiens</i>	59
113466	4	7670	acagcgagtgactcagaaca	28	<i>H. sapiens</i>	60
113468	11	1048	catgcagagcaggggtgggcc	30	<i>H. sapiens</i>	61



Western blot analysis (immunoblot analysis) is carried out using standard methods. Cells are harvested 16-20 h after oligonucleotide treatment, washed once with PBS, suspended in Laemmli buffer (100 ul/well), boiled for 5 minutes and loaded on a 16% SDS-PAGE gel. Gels are run for 1.5 hours at 150 V, and transferred to membrane for western blotting. Appropriate primary antibody directed to SMRT is used, with a radiolabeled or fluorescently labeled secondary antibody directed against the primary antibody species. Bands are visualized using a PHOSPHORIMAGER™ (Molecular Dynamics, Sunnyvale CA).

**What is claimed is:**

1. A compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding SMRT, wherein said compound specifically hybridizes with said nucleic acid molecule encoding SMRT and inhibits the expression of SMRT.
2. The compound of claim 1 which is an antisense oligonucleotide.
3. The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.
4. The compound of claim 3 wherein the modified internucleoside linkage is a phosphorothioate linkage.
5. The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified sugar moiety.
6. The compound of claim 5 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.
7. The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified nucleobase.
8. The compound of claim 7 wherein the modified nucleobase is a 5-methylcytosine.
9. The compound of claim 2 wherein the antisense oligonucleotide is a chimeric oligonucleotide.
10. A compound 8 to 80 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of a preferred target region on a nucleic acid molecule encoding SMRT.
11. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.
12. The composition of claim 11 further comprising a colloidal dispersion system.
13. The composition of claim 11 wherein the compound is an antisense oligonucleotide.
14. A method of inhibiting the expression of SMRT in cells or tissues comprising contacting said cells or tissues

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with the compound of claim 1 so that expression of SMRT is inhibited.

15. A method of treating an animal having a disease or condition associated with SMRT comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claim 1 so that expression of SMRT is inhibited.

16. The method of claim 15 wherein the disease or condition is an inflammatory disorder.

17. The method of claim 16 wherein the inflammatory disorder is rheumatoid arthritis.

18. The method of claim 15 wherein the disease or condition is a hyperproliferative disorder.

19. The method of claim 18 wherein the hyperproliferative disorder is cancer.

20. The method of claim 19 wherein the cancer is selected from the group consisting of leukemia and breast cancer.

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ABSTRACT

5

Antisense compounds, compositions and methods are provided for modulating the expression of SMRT. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding SMRT. Methods of using these compounds for modulation of SMRT expression and for treatment of diseases associated with expression of SMRT are provided.

10

DOCKET NO.: PTS-0012

"Express Mail" Label No.: EL918916361US  
Date of Deposit: 6/17/2002

## COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **Antisense Modulation of SMRT Expression** the specification of which:

(XX) is attached hereto.

( ) was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to the patentability of this application in accordance with 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a-d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

Country	Number	Date Filed	Priority Claimed	
			Yes	No
			Yes	No
			Yes	No

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented)

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Provisional Application No.	Filing Date

DOCKET NO.: PTS-0012

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Herb Boswell, Registration No. 27,311; Laurel Spear Bernstein, Registration No. 37,280; Neil S. Bartfeld, Registration No. 39,901; and April C. Logan, Registration No. 33,950, of Isis Pharmaceuticals, Inc.; and Jane Massey Licata, Registration No. 32,257, and Kathleen A. Tyrrell, Registration No. 38,350 of the firm of Licata and Tyrrell P.C., 66 East Main Street, Marlton NJ 08053.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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	Post Office Address:same as above		
3	Full Name: Kenneth W. Dobie	Inventor's Signature: <i>Kenneth W. Dobie</i>	Date: 5/23/02
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	Post Office Address: same as above		

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SEQUENCE LISTING

<110> C. Frank Bennett  
Susan M. Freier  
Kenneth W. Dobie

<120> ANTISENSE MODULATION OF SMRT EXPRESSION

<130> PTS-0012

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15

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Pro Gly Ser Ile Ile Gln Pro Gln Arg Arg Arg Pro Ser Leu Leu Ser	
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Ile Glu Ser Lys Arg Pro Arg Leu Glu Leu Leu Pro Asp Pro Leu Leu	
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440 445 450	

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Gly	Arg	Lys	Thr	Ala	Asn	Ser	Gln	Gly	Arg	Arg	Lys	Gly	Arg	Ile	Thr	
			570						575				580			
cgc	tca	atg	gct	aat	gag	gcc	aac	agc	gag	gag	gcc	atc	acc	ccc	cag	1950
Arg	Ser	Met	Ala	Asn	Glu	Ala	Asn	Ser	Glu	Glu	Ala	Ile	Thr	Pro	Gln	
			585					590				595				
cag	agc	gcc	gag	ctg	gcc	tcc	atg	gag	ctg	aat	gag	agt	tct	cgc	tgg	1998
Gln	Ser	Ala	Glu	Leu	Ala	Ser	Met	Glu	Leu	Asn	Glu	Ser	Ser	Arg	Trp	
			600				605				610					
aca	gaa	gaa	gaa	atg	gaa	aca	gcc	aag	aaa	ggt	ctc	ctg	gaa	cac	ggc	2046
Thr	Glu	Glu	Glu	Met	Glu	Thr	Ala	Lys	Lys	Gly	Leu	Leu	Glu	His	Gly	
615					620					625					630	
cgc	aac	tgg	tcg	gcc	atc	gcc	cgg	atg	gtg	ggc	tcc	aag	act	gtg	tcg	2094
Arg	Asn	Trp	Ser	Ala	Ile	Ala	Arg	Met	Val	Gly	Ser	Lys	Thr	Val	Ser	
				635					640					645		
cag	tgt	aag	aac	ttc	tac	ttc	aac	tac	aag	aag	agg	cag	aac	ctc	gat	2142
Gln	Cys	Lys	Asn	Phe	Tyr	Phe	Asn	Tyr	Lys	Lys	Arg	Gln	Asn	Leu	Asp	
			650						655				660			

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PATENT

gag atc ttg cag cag cac aag ctg aag atg gag aag gag agg aac gcg	2190
Glu Ile Leu Gln Gln His Lys Leu Lys Met Glu Lys Glu Arg Asn Ala	
665 670 675	
cgg agg aag aag aag aaa gcg ccg gcg gcg gcc agc gag gag gct gca	2238
Arg Arg Lys Lys Lys Lys Ala Pro Ala Ala Ala Ser Glu Glu Ala Ala	
680 685 690	
ttc ccg ccc gtg gtg gag gat gag gag atg gag gcg tcg ggc gtg acg	2286
Phe Pro Pro Val Val Glu Asp Glu Glu Met Glu Ala Ser Gly Val Thr	
695 700 705 710	
gga aat gag gag gag atg gtg gag gag gct gaa gcc act gtc aac aac	2334
Gly Asn Glu Glu Glu Met Val Glu Glu Ala Glu Ala Thr Val Asn Asn	
715 720 725	
agc tca gac acc gag agc atc ccc tct cct cac act gag gcc gcc aag	2382
Ser Ser Asp Thr Glu Ser Ile Pro Ser Pro His Thr Glu Ala Ala Lys	
730 735 740	
gac aca ggg cag aat ggg ccc aag ccc cca gcc acc ctg ggc gcc gac	2430
Asp Thr Gly Gln Asn Gly Pro Lys Pro Pro Ala Thr Leu Gly Ala Asp	
745 750 755	
ggg cca ccc cca ggg cca ccc acc cca cca ccg gag gac atc ccg gcc	2478
Gly Pro Pro Pro Gly Pro Pro Thr Pro Pro Pro Glu Asp Ile Pro Ala	
760 765 770	
ccc act gag tcc acc ccg gcc tct gaa gcc acc tta gcc cct acg ccc	2526
Pro Thr Glu Ser Thr Pro Ala Ser Glu Ala Thr Leu Ala Pro Thr Pro	
775 780 785 790	
cca cca gca ccc cca ttt ccc tct tca cct cct cct gtg gtc ccc aag	2574
Pro Pro Ala Pro Pro Phe Pro Ser Ser Pro Pro Pro Val Val Pro Lys	
795 800 805	
gag gag aag gag gag gag acc gca gca gcg ccc cca gtg gag gag ggg	2622
Glu Glu Lys Glu Glu Glu Thr Ala Ala Ala Pro Pro Val Glu Glu Gly	
810 815 820	
gag gag cag aag ccc ccc gcg gct gag gag ctg gca gtg gac aca ggg	2670
Glu Glu Gln Lys Pro Pro Ala Ala Glu Glu Leu Ala Val Asp Thr Gly	
825 830 835	
aag gcc gag gag ccc gtc aag agc gag tgc acg gag gaa gcc gag gag	2718
Lys Ala Glu Glu Pro Val Lys Ser Glu Cys Thr Glu Glu Ala Glu Glu	
840 845 850	
ggg ccg gcc aag ggc aag gac gcg gag gcc gct gag gcc acg gcc gag	2766
Gly Pro Ala Lys Gly Lys Asp Ala Glu Ala Ala Glu Ala Thr Ala Glu	
855 860 865 870	

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PATENT

agg gcg ctc aag gca gag aag aag gag ggc ggg agc ggc agg gcc acc	2814
Arg Ala Leu Lys Ala Glu Lys Lys Glu Gly Gly Ser Gly Arg Ala Thr	
875 880 885	
aca gcc aag agc tcg ggc gcc ccc cag gac agc gac tcc agt gcc acc	2862
Thr Ala Lys Ser Ser Gly Ala Pro Gln Asp Ser Asp Ser Ser Ala Thr	
890 895 900	
tgc agt gca gac gag gtg gat gag gcc gag ggc ggc gac aag aac cgg	2910
Cys Ser Ala Asp Glu Val Asp Glu Ala Glu Gly Gly Asp Lys Asn Arg	
905 910 915	
ctg ctg tcc cca agg ccc agc ctc ctc acc ccg act ggc gac ccc cgg	2958
Leu Leu Ser Pro Arg Pro Ser Leu Leu Thr Pro Thr Gly Asp Pro Arg	
920 925 930	
gcc aat gcc tca ccc cag aag cca ctg gac ctg aag cag ctg aag cag	3006
Ala Asn Ala Ser Pro Gln Lys Pro Leu Asp Leu Lys Gln Leu Lys Gln	
935 940 945 950	
cga gcg gct gcc atc ccc ccc atc cag gtc acc aaa gtc cat gag ccc	3054
Arg Ala Ala Ala Ile Pro Pro Ile Gln Val Thr Lys Val His Glu Pro	
955 960 965	
ccc cgg gag gac gca gct ccc acc aag cca gct ccc cca gcc cca ccg	3102
Pro Arg Glu Asp Ala Ala Pro Thr Lys Pro Ala Pro Pro Ala Pro Pro	
970 975 980	
cca ccg caa aac ctg cag ccg gag agc gac gcc cct cag cag cct ggc	3150
Pro Pro Gln Asn Leu Gln Pro Glu Ser Asp Ala Pro Gln Gln Pro Gly	
985 990 995	
agc agc ccc cgg ggc aag agc agg agc ccg gca ccc ccc gcc gac aag	3198
Ser Ser Pro Arg Gly Lys Ser Arg Ser Pro Ala Pro Pro Ala Asp Lys	
1000 1005 1010	
gag gca gag aag cct gtg ttc ttc cca gcc ttc gca gcc gag gcc cag	3246
Glu Ala Glu Lys Pro Val Phe Phe Pro Ala Phe Ala Ala Glu Ala Gln	
1015 1020 1025 1030	
aag ctg cct ggg gac ccc cct tgc tgg act tcc ggc ctg ccc ttc ccc	3294
Lys Leu Pro Gly Asp Pro Pro Cys Trp Thr Ser Gly Leu Pro Phe Pro	
1035 1040 1045	
gtg ccc ccc cgt gag gtg atc aag gcc tcc ccg cat gcc ccg gac ccc	3342
Val Pro Pro Arg Glu Val Ile Lys Ala Ser Pro His Ala Pro Asp Pro	
1050 1055 1060	
tca gcc ttc tcc tac gct cca cct ggt cac cca ctg ccc ctg ggc ctc	3390
Ser Ala Phe Ser Tyr Ala Pro Pro Gly His Pro Leu Pro Leu Gly Leu	
1065 1070 1075	

cat	gac	act	gcc	cgg	ccc	gtc	ctg	ccg	cgc	cca	ccc	acc	atc	tcc	aac	3438
His	Asp	Thr	Ala	Arg	Pro	Val	Leu	Pro	Arg	Pro	Pro	Thr	Ile	Ser	Asn	
1080						1085					1090					
ccg	cct	ccc	ctc	atc	tcc	tct	gcc	aag	cac	ccc	agc	gtc	ctc	gag	agg	3486
Pro	Pro	Pro	Leu	Ile	Ser	Ser	Ala	Lys	His	Pro	Ser	Val	Leu	Glu	Arg	
1095					1100				1105					1110		
caa	ata	ggt	gcc	atc	tcc	caa	gga	atg	tcg	gtc	cag	ctc	cac	gtc	ccg	3534
Gln	Ile	Gly	Ala	Ile	Ser	Gln	Gly	Met	Ser	Val	Gln	Leu	His	Val	Pro	
				1115					1120				1125			
tac	tca	gag	cat	gcc	aag	gcc	ccg	gtg	ggc	cct	gtc	acc	atg	ggg	ctg	3582
Tyr	Ser	Glu	His	Ala	Lys	Ala	Pro	Val	Gly	Pro	Val	Thr	Met	Gly	Leu	
				1130				1135				1140				
ccc	ctg	ccc	atg	gac	ccc	aaa	aag	ctg	gca	ccc	ttc	agc	gga	gtg	aag	3630
Pro	Leu	Pro	Met	Asp	Pro	Lys	Lys	Leu	Ala	Pro	Phe	Ser	Gly	Val	Lys	
				1145			1150				1155					
cag	gag	cag	ctg	tcc	cca	cgg	ggc	cag	gct	ggg	cca	ccg	gag	agc	ctg	3678
Gln	Glu	Gln	Leu	Ser	Pro	Arg	Gly	Gln	Ala	Gly	Pro	Pro	Glu	Ser	Leu	
				1160			1165				1170					
ggg	gtg	ccc	aca	gcc	cag	gag	gcg	tcc	gtg	ctg	aga	ggg	aca	gct	ctg	3726
Gly	Val	Pro	Thr	Ala	Gln	Glu	Ala	Ser	Val	Leu	Arg	Gly	Thr	Ala	Leu	
1175					1180				1185				1190			
ggc	tca	gtt	ccg	ggc	gga	agc	atc	acc	aaa	ggc	att	ccc	agc	aca	cgg	3774
Gly	Ser	Val	Pro	Gly	Gly	Ser	Ile	Thr	Lys	Gly	Ile	Pro	Ser	Thr	Arg	
				1195					1200				1205			
gtg	ccc	tcg	gac	agc	gcc	atc	aca	tac	cgc	ggc	tcc	atc	acc	cac	ggc	3822
Val	Pro	Ser	Asp	Ser	Ala	Ile	Thr	Tyr	Arg	Gly	Ser	Ile	Thr	His	Gly	
				1210					1215				1220			
acg	cca	gct	gac	gtc	ctg	tac	aag	ggc	acc	atc	acc	agg	atc	atc	ggc	3870
Thr	Pro	Ala	Asp	Val	Leu	Tyr	Lys	Gly	Thr	Ile	Thr	Arg	Ile	Ile	Gly	
				1225				1230				1235				
gag	gac	agc	ccg	agt	cgc	ttg	gac	cgc	ggc	cgg	gag	gac	agc	ctg	ccc	3918
Glu	Asp	Ser	Pro	Ser	Arg	Leu	Asp	Arg	Gly	Arg	Glu	Asp	Ser	Leu	Pro	
				1240				1245			1250					
aag	ggc	cac	gtc	atc	tac	gaa	ggc	aag	aag	ggc	cac	gtc	ttg	tcc	tat	3966
Lys	Gly	His	Val	Ile	Tyr	Glu	Gly	Lys	Lys	Gly	His	Val	Leu	Ser	Tyr	
1255					1260				1265				1270			
gag	ggt	ggc	atg	tct	gtg	acc	cag	tgc	tcc	aag	gag	gac	ggc	aga	agc	4014
Glu	Gly	Gly	Met	Ser	Val	Thr	Gln	Cys	Ser	Lys	Glu	Asp	Gly	Arg	Ser	
				1275												

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agc tca gga ccc ccc cat gag acg gcc gcc ccc aag cgc acc tat gac	4062
Ser Ser Gly Pro Pro His Glu Thr Ala Ala Pro Lys Arg Thr Tyr Asp	
1290 1295 1300	
atg atg gag ggc cgc gtg ggc aga gcc atc tcc tca gcc agc atc gaa	4110
Met Met Glu Gly Arg Val Gly Arg Ala Ile Ser Ser Ala Ser Ile Glu	
1305 1310 1315	
ggt ctc atg ggc cgt gcc atc ccg ccg gag cga cac agc ccc cac cac	4158
Gly Leu Met Gly Arg Ala Ile Pro Pro Glu Arg His Ser Pro His His	
1320 1325 1330	
ctc aaa gag cag cac cac atc cgc ggg tcc atc aca caa ggg atc cct	4206
Leu Lys Glu Gln His His Ile Arg Gly Ser Ile Thr Gln Gly Ile Pro	
1335 1340 1345 1350	
cgg tcc tac gtg gag gca cag gag gac tac ctg cgt cgg gag gcc aag	4254
Arg Ser Tyr Val Glu Ala Gln Glu Asp Tyr Leu Arg Arg Glu Ala Lys	
1355 1360 1365	
ctc cta aag cgg gag ggc acg cct ccg ccc cca ccg ccc tca cgg gac	4302
Leu Leu Lys Arg Glu Gly Thr Pro Pro Pro Pro Pro Pro Ser Arg Asp	
1370 1375 1380	
ctg acc gag gcc tac aag acg cag gcc ctg ggc ccc ctg aag ctg aag	4350
Leu Thr Glu Ala Tyr Lys Thr Gln Ala Leu Gly Pro Leu Lys Leu Lys	
1385 1390 1395	
ccg gcc cat gag ggc ctg gtg gcc acg gtg aag gag gcg ggc cgc tcc	4398
Pro Ala His Glu Gly Leu Val Ala Thr Val Lys Glu Ala Gly Arg Ser	
1400 1405 1410	
atc cat gag atc ccg cgc gag gag ctg cgg cac acg ccc gag ctg ccc	4446
Ile His Glu Ile Pro Arg Glu Glu Leu Arg His Thr Pro Glu Leu Pro	
1415 1420 1425 1430	
ctg gcc ccg cgg ccg ctc aag gag ggc tcc atc acg cag ggc acc ccg	4494
Leu Ala Pro Arg Pro Leu Lys Glu Gly Ser Ile Thr Gln Gly Thr Pro	
1435 1440 1445	
ctc aag tac gac acc ggc gcg tcc acc act ggc tcc aaa aag cac gac	4542
Leu Lys Tyr Asp Thr Gly Ala Ser Thr Thr Gly Ser Lys Lys His Asp	
1450 1455 1460	
gta cgc tcc ctc atc ggc agc ccc ggc cgg acg ttc cca ccc gtg cac	4590
Val Arg Ser Leu Ile Gly Ser Pro Gly Arg Thr Phe Pro Pro Val His	
1465 1470 1475	
ccg ctg gat gtg atg gcc gac gcc cgg gca ctg gaa cgt gcc tgc tac	4638
Pro Leu Asp Val Met Ala Asp Ala Arg Ala Leu Glu Arg Ala Cys Tyr	
1480 1485 1490	

gag gag agc ctg aag agc cgg cca ggg acc gcc agc agc tcg ggg ggc 4686  
 Glu Glu Ser Leu Lys Ser Arg Pro Gly Thr Ala Ser Ser Ser Gly Gly  
 1495 1500 1505 1510  
 tcc att gcg cgc ggc gcc ccg gtc att gtg cct gag ctg ggt aag ccg 4734  
 Ser Ile Ala Arg Gly Ala Pro Val Ile Val Pro Glu Leu Gly Lys Pro  
 1515 1520 1525  
 cgg cag agc ccc ctg acc tat gag gac cac ggg gca ccc ttt gcc ggc 4782  
 Arg Gln Ser Pro Leu Thr Tyr Glu Asp His Gly Ala Pro Phe Ala Gly  
 1530 1535 1540  
 cac ctc cca cga ggt tcg ccc gtg acc atg cgg gag ccc acg ccg cgc 4830  
 His Leu Pro Arg Gly Ser Pro Val Thr Met Arg Glu Pro Thr Pro Arg  
 1545 1550 1555  
 ctg cag gag ggc agc ctt tcg tcc agc aag gca tcc cag gac cga aag 4878  
 Leu Gln Glu Gly Ser Leu Ser Ser Ser Lys Ala Ser Gln Asp Arg Lys  
 1560 1565 1570  
 ctg acg tcg acg cct cgt gag atc gcc aag tcc ccg cac agc acc gtg 4926  
 Leu Thr Ser Thr Pro Arg Glu Ile Ala Lys Ser Pro His Ser Thr Val  
 1575 1580 1585 1590  
 ccc gag cac cac cca cac ccc atc tcg ccc tat gag cac ctg ctt cgg 4974  
 Pro Glu His His Pro His Pro Ile Ser Pro Tyr Glu His Leu Leu Arg  
 1595 1600 1605  
 ggc gtg agt ggc gtg gac ctg tat cgc agc cac atc ccc ctg gcc ttc 5022  
 Gly Val Ser Gly Val Asp Leu Tyr Arg Ser His Ile Pro Leu Ala Phe  
 1610 1615 1620  
 gac ccc acc tcc ata ccc cgc ggc atc cct ctg gac gca gcc gct gcc 5070  
 Asp Pro Thr Ser Ile Pro Arg Gly Ile Pro Leu Asp Ala Ala Ala Ala  
 1625 1630 1635  
 tac tac ctg ccc cga cac ctg gcc ccc aac ccc acc tac ccg cac ctg 5118  
 Tyr Tyr Leu Pro Arg His Leu Ala Pro Asn Pro Thr Tyr Pro His Leu  
 1640 1645 1650  
 tac cca ccc tac ctc atc cgc ggc tac ccc gac acg gcg gcg ctg gag 5166  
 Tyr Pro Pro Tyr Leu Ile Arg Gly Tyr Pro Asp Thr Ala Ala Leu Glu  
 1655 1660 1665 1670  
 aac cgg cag acc atc atc aat gac tac atc acc tcg cag cag atg cac 5214  
 Asn Arg Gln Thr Ile Ile Asn Asp Tyr Ile Thr Ser Gln Gln Met His  
 1675 1680 1685  
 cac aac acg gcc acc gcc atg gcc cag cga gct gat atg ctg agg ggc 5262  
 His Asn Thr Ala Thr Ala Met Ala Gln Arg Ala Asp Met Leu Arg Gly  
 1690 1695 1700



ctc	tcg	ccc	cgc	gag	tcc	tcg	ctg	gca	ctc	aac	tac	gct	gcg	ggc	ccc	5310
Leu	Ser	Pro	Arg	Glu	Ser	Ser	Leu	Ala	Leu	Asn	Tyr	Ala	Ala	Gly	Pro	
1705				1710				1715								
cga	ggc	atc	atc	gac	ctg	tcc	caa	gtg	cca	cac	ctg	cct	gtg	ctc	gtg	5358
Arg	Gly	Ile	Ile	Asp	Leu	Ser	Gln	Val	Pro	His	Leu	Pro	Val	Leu	Val	
1720				1725				1730								
ccc	ccg	aca	cca	ggc	acc	cca	gcc	acc	gcc	atg	gac	cgc	ctt	gcc	tac	5406
Pro	Pro	Thr	Pro	Gly	Thr	Pro	Ala	Thr	Ala	Met	Asp	Arg	Leu	Ala	Tyr	
1735				1740				1745				1750				
ctc	ccc	acc	gcg	ccc	cag	ccc	ttc	agc	agc	cgc	cac	agc	agc	tcc	cca	5454
Leu	Pro	Thr	Ala	Pro	Gln	Pro	Phe	Ser	Ser	Arg	His	Ser	Ser	Ser	Pro	
1755				1760				1765								
ctc	tcc	cca	gga	ggc	cca	aca	cac	ttg	aca	aaa	cca	acc	acc	acg	tcc	5502
Leu	Ser	Pro	Gly	Gly	Pro	Thr	His	Leu	Thr	Lys	Pro	Thr	Thr	Thr	Ser	
1770				1775				1780								
tcg	tcc	gag	cgg	gag	cga	gac	cgg	gat	cga	gag	cgg	gac	cgg	gat	cgg	5550
Ser	Ser	Glu	Arg	Glu	Arg	Asp	Arg	Asp	Arg	Glu	Arg	Asp	Arg	Asp	Arg	
1785				1790				1795								
gag	cgg	gaa	aag	tcc	atc	ctc	acg	tcc	acc	acg	acg	gtg	gag	cac	gca	5598
Glu	Arg	Glu	Lys	Ser	Ile	Leu	Thr	Ser	Thr	Thr	Thr	Val	Glu	His	Ala	
1800				1805				1810								
ccc	atc	tgg	aga	cct	ggc	aca	gag	cag	agc	agc	ggc	agc	agc	ggc	agc	5646
Pro	Ile	Trp	Arg	Pro	Gly	Thr	Glu	Gln	Ser	Ser	Gly	Ser	Ser	Gly	Ser	
1815				1820				1825				1830				
agc	ggc	ggg	ggc	ggg	ggc	agc	agc	agc	cgc	ccc	gcc	tcc	cac	tcc	cat	5694
Ser	Gly	Gly	Gly	Gly	Gly	Ser	Ser	Ser	Arg	Pro	Ala	Ser	His	Ser	His	
1835				1840				1845								
gcc	cac	cag	cac	tcg	ccc	atc	tcc	cct	cgg	acc	cag	gat	gcc	ctc	cag	5742
Ala	His	Gln	His	Ser	Pro	Ile	Ser	Pro	Arg	Thr	Gln	Asp	Ala	Leu	Gln	
1850				1855				1860								
cag	aga	ccc	agt	gtg	ctt	cac	aac	aca	ggc	atg	aag	ggc	atc	atc	acc	5790
Gln	Arg	Pro	Ser	Val	Leu	His	Asn	Thr	Gly	Met	Lys	Gly	Ile	Ile	Thr	
1865				1870				1875								
gct	gtg	gag	ccc	agc	aag	ccc	acg	gtc	ctg	agg	tcc	acc	tcc	acc	tcc	5838
Ala	Val	Glu	Pro	Ser	Lys	Pro	Thr	Val	Leu	Arg	Ser	Thr	Ser	Thr	Ser	
1880				1885				1890								
tca	ccc	gtt	cgc	cca	gct	gcc	aca	ttc	cca	cct	gcc	acc	cac	tgc	cca	5886
Ser	Pro	Val	Arg	Pro	Ala	Ala	Thr	Phe	Pro	Pro	Ala	Thr	His	Cys	Pro	
1895				1900				1905				1910				

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ctg ggc ggc acc ctc gat ggg gtc tac cct acc ctc atg gag ccc gtc	5934
Leu Gly Gly Thr Leu Asp Gly Val Tyr Pro Thr Leu Met Glu Pro Val	
1915 1920 1925	
ttg ctg ccc aag gag gcc ccc cgg gtc gcc cgg cca gag cgg ccc cga	5982
Leu Leu Pro Lys Glu Ala Pro Arg Val Ala Arg Pro Glu Arg Pro Arg	
1930 1935 1940	
gca gac acc ggc cat gcc ttc ctc gcc aag ccc cca gcc cgc tcc ggg	6030
Ala Asp Thr Gly His Ala Phe Leu Ala Lys Pro Pro Ala Arg Ser Gly	
1945 1950 1955	
ctg gag ccc gcc tcc tcc ccc agc aag ggc tcg gag ccc cgg ccc cta	6078
Leu Glu Pro Ala Ser Ser Pro Ser Lys Gly Ser Glu Pro Arg Pro Leu	
1960 1965 1970	
gtg cct cct gtc tct ggc cac gcc acc atc gcc cgc acc cct gcg aag	6126
Val Pro Pro Val Ser Gly His Ala Thr Ile Ala Arg Thr Pro Ala Lys	
1975 1980 1985 1990	
aac ctc gca cct cac cac gcc agc ccg gac ccg ccg gcg cca cct gcc	6174
Asn Leu Ala Pro His His Ala Ser Pro Asp Pro Pro Ala Pro Pro Ala	
1995 2000 2005	
tcg gcc tcg gac ccg cac cgg gaa aag act caa agt aaa ccc ttt tcc	6222
Ser Ala Ser Asp Pro His Arg Glu Lys Thr Gln Ser Lys Pro Phe Ser	
2010 2015 2020	
atc cag gaa ctg gaa ctc cgt tct ctg ggt tac cac ggc agc agc tac	6270
Ile Gln Glu Leu Glu Leu Arg Ser Leu Gly Tyr His Gly Ser Ser Tyr	
2025 2030 2035	
agc ccc gaa ggg gtg gag ccc gtc agc cct gtg agc tca ccc agt ctg	6318
Ser Pro Glu Gly Val Glu Pro Val Ser Pro Val Ser Ser Pro Ser Leu	
2040 2045 2050	
acc cac gac aag ggg ctc ccc aag cac ctg gaa gag ctc gac aag agc	6366
Thr His Asp Lys Gly Leu Pro Lys His Leu Glu Glu Leu Asp Lys Ser	
2055 2060 2065 2070	
cac ctg gag ggg gag ctg cgg ccc aag cag cca ggc ccc gtg aag ctt	6414
His Leu Glu Gly Glu Leu Arg Pro Lys Gln Pro Gly Pro Val Lys Leu	
2075 2080 2085	
ggc ggg gag gcc gcc cac ctc cca cac ctg cgg ccg ctg cct gag agc	6462
Gly Gly Glu Ala Ala His Leu Pro His Leu Arg Pro Leu Pro Glu Ser	
2090 2095 2100	
cag ccc tcg tcc agc ccg ctg ctc cag acc gcc cca ggg gtc aaa ggt	6510
Gln Pro Ser Ser Ser Pro Leu Leu Gln Thr Ala Pro Gly Val Lys Gly	
2105 2110 2115	

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PATENT

cac cag cgg gtg gtc acc ctg gcc cag cac atc agt gag gtc atc aca	6558
His Gln Arg Val Val Thr Leu Ala Gln His Ile Ser Glu Val Ile Thr	
2120 2125 2130	
cag gac tac acc cgg cac cac cca cag cag ctc agc gca ccc ctg ccc	6606
Gln Asp Tyr Thr Arg His His Pro Gln Gln Leu Ser Ala Pro Leu Pro	
2135 2140 2145 2150	
gcc ccc ctc tac tcc ttc cct ggg gcc agc tgc ccc gtc ctg gac ctc	6654
Ala Pro Leu Tyr Ser Phe Pro Gly Ala Ser Cys Pro Val Leu Asp Leu	
2155 2160 2165	
cgc cgc cca ccc agt gac ctc tac ctc ccg ccc ccg gac cat ggt gcc	6702
Arg Arg Pro Pro Ser Asp Leu Tyr Leu Pro Pro Pro Asp His Gly Ala	
2170 2175 2180	
ccg gcc cgt ggc tcc ccc cac agc gaa ggg ggc aag agg tct cca gag	6750
Pro Ala Arg Gly Ser Pro His Ser Glu Gly Gly Lys Arg Ser Pro Glu	
2185 2190 2195	
cca aac aag acg tcg gtc ttg ggt ggt ggt gag gac ggt att gaa cct	6798
Pro Asn Lys Thr Ser Val Leu Gly Gly Gly Glu Asp Gly Ile Glu Pro	
2200 2205 2210	
gtg tcc cca ccg gag ggc atg acg gag cca ggg cac tcc cgg agt gct	6846
Val Ser Pro Pro Glu Gly Met Thr Glu Pro Gly His Ser Arg Ser Ala	
2215 2220 2225 2230	
gtg tac ccg ctg ctg tac cgg gat ggg gaa cag acg gag ccc agc agg	6894
Val Tyr Pro Leu Leu Tyr Arg Asp Gly Glu Gln Thr Glu Pro Ser Arg	
2235 2240 2245	
atg ggc tcc aag tct cca ggc aac acc agc cag ccg cca gcc ttc ttc	6942
Met Gly Ser Lys Ser Pro Gly Asn Thr Ser Gln Pro Pro Ala Phe Phe	
2250 2255 2260	
agc aag ctg acc gag agc aac tcc gcc atg gtc aag tcc aag aag caa	6990
Ser Lys Leu Thr Glu Ser Asn Ser Ala Met Val Lys Ser Lys Lys Gln	
2265 2270 2275	
gag atc aac aag aag ctg aac acc cac aac cgg aat gag cct gaa tac	7038
Glu Ile Asn Lys Lys Leu Asn Thr His Asn Arg Asn Glu Pro Glu Tyr	
2280 2285 2290	
aat atc agc cag cct ggg acg gag atc ttc aat atg ccc gcc atc acc	7086
Asn Ile Ser Gln Pro Gly Thr Glu Ile Phe Asn Met Pro Ala Ile Thr	
2295 2300 2305 2310	
gga aca ggc ctt atg acc tat aga agc cag gcg gtg cag gaa cat gcc	7134
Gly Thr Gly Leu Met Thr Tyr Arg Ser Gln Ala Val Gln Glu His Ala	
2315 2320 2325	

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agc acc aac atg ggg ctg gag gcc ata att aga aag gca ctc atg ggt 7182  
 Ser Thr Asn Met Gly Leu Glu Ala Ile Ile Arg Lys Ala Leu Met Gly  
 2330 2335 2340  
 aaa tat gac cag tgg gaa gag tcc ccg ccg ctc agc gcc aat gct ttt 7230  
 Lys Tyr Asp Gln Trp Glu Glu Ser Pro Pro Leu Ser Ala Asn Ala Phe  
 2345 2350 2355  
 aac cct ctg aat gcc agt gcc agc ctg ccc gct gct atg ccc ata acc 7278  
 Asn Pro Leu Asn Ala Ser Ala Ser Leu Pro Ala Ala Met Pro Ile Thr  
 2360 2365 2370  
 gct gct gac gga cgg agt gac cac aca ctc acc tcg cca ggt ggc ggc 7326  
 Ala Ala Asp Gly Arg Ser Asp His Thr Leu Thr Ser Pro Gly Gly Gly  
 2375 2380 2385 2390  
 ggg aag gcc aag gtc tct ggc aga ccc agc agc cga aaa gcc aag tcc 7374  
 Gly Lys Ala Lys Val Ser Gly Arg Pro Ser Ser Arg Lys Ala Lys Ser  
 2395 2400 2405  
 ccg gcc ccg ggc ctg gca tct ggg gac cgg cca ccc tct gtc tcc tca 7422  
 Pro Ala Pro Gly Leu Ala Ser Gly Asp Arg Pro Pro Ser Val Ser Ser  
 2410 2415 2420  
 gtg cac tcg gag gga gac tgc aac cgc cgg acg ccg ctc acc aac cgc 7470  
 Val His Ser Glu Gly Asp Cys Asn Arg Arg Thr Pro Leu Thr Asn Arg  
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 2440 2445 2450  
 aac ccc ctg atc atg cgg ctg cag gcg ggt gtc atg gct tcc cca ccc 7566  
 Asn Pro Leu Ile Met Arg Leu Gln Ala Gly Val Met Ala Ser Pro Pro  
 2455 2460 2465 2470  
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 Pro Pro Gly Leu Pro Ala Gly Ser Gly Pro Leu Ala Gly Pro His His  
 2475 2480 2485  
 gcc tgg gac gag gag ccc aag cca ctg ctc tgc tcg cag tac gag aca 7662  
 Ala Trp Asp Glu Glu Pro Lys Pro Leu Leu Cys Ser Gln Tyr Glu Thr  
 2490 2495 2500  
 ctc tcc gac agc gag tga ctccagaacag ggcggggggg ggcggggcggt gtcaggtccc 7720  
 Leu Ser Asp Ser Glu  
 2505  
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 aggagcccct gagtcgcct gcgcctccat ccattctgtcc gtccagagcc ggcattcctg 7840  
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18

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<211> 29

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<220>

<223> PCR Primer

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29

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PATENT

&lt;210&gt; 7

&lt;211&gt; 30

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR Probe

&lt;400&gt; 7

tgggaaggaa aggcagatgt aaatgatgtg

30

&lt;210&gt; 8

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR Primer

&lt;400&gt; 8

gaaggtgaag gtcggagtc

19

&lt;210&gt; 9

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR Primer

&lt;400&gt; 9

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<213> Artificial Sequence
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20

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<400> 11

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Met Ser Gly Ser Thr Gln Leu Val Ala Gln Thr Trp Arg Ala Thr Glu

**1                      5                      10                      15**

ccc cgc tac ccg ccc cac agc ctt tcc tac cca gtg cag atc gcc cgg 97

Pro Arg Tyr Pro Pro His Ser Leu Ser Tyr Pro Val Gln Ile Ala Arg

**20**                      **25**                      **30**

acg cac acg gac gtc ggg ctc ctg gag tac cag cac cac tcc cgc gac 145

Thr His Thr Asp Val Gly Leu Leu Glu Tyr Gln His His Ser Arg Asp

**35                      40                      45**

tat gcc tcc cac ctg tcg ccg ggc tcc atc atc cag ccc cag cgg cgg 193

Tyr Ala Ser His Leu Ser Pro Gly Ser Ile Ile Gln Pro Gln Arg Arg

**50                          55                          60**

agg ccc tcc ctg ctg tct gag ttç cag ccc ggg aat gaa cgg tcc cag 241

Arg	Pro	Ser	Leu	Leu	Ser	Glu	Phe	Gln	Pro	Gly	Asn	Glu	Arg	Ser	Gln	
65					70				75						80	
gag	ctc	cac	ctg	cgg	cca	gag	tcc	cac	tca	tac	ctg	ccc	gag	ctg	ggg	289
Glu	Leu	His	Leu	Arg	Pro	Glu	Ser	His	Ser	Tyr	Leu	Pro	Glu	Leu	Gly	
				85					90						95	
aag	tca	gag	atg	gag	ttc	att	gaa	agc	aag	cgc	cct	cgg	cta	gag	ctg	337
Lys	Ser	Glu	Met	Glu	Phe	Ile	Glu	Ser	Lys	Arg	Pro	Arg	Leu	Glu	Leu	
			100						105						110	
ctg	cct	gac	ccc	ctg	ctg	cga	ccg	tca	ccc	ctg	ctg	gcc	acg	ggc	cag	385
Leu	Pro	Asp	Pro	Leu	Leu	Arg	Pro	Ser	Pro	Leu	Leu	Ala	Thr	Gly	Gln	
			115						120						125	
cct	gcg	gga	tct	gaa	gac	ctc	acc	aag	gac	cgt	agc	ctg	acg	ggc	aag	433
Pro	Ala	Gly	Ser	Glu	Asp	Leu	Thr	Lys	Asp	Arg	Ser	Leu	Thr	Gly	Lys	
	130						135								140	
ctg	gaa	ccg	gtg	tct	ccc	ccc	agc	ccc	ccg	cac	act	gac	cct	gag	ctg	481
Leu	Glu	Pro	Val	Ser	Pro	Pro	Ser	Pro	Pro	His	Thr	Asp	Pro	Glu	Leu	
145					150					155					160	
gag	ctg	gtg	ccg	cca	cgg	ctg	tcc	aag	gag	gag	ctg	atc	cag	aac	atg	529
Glu	Leu	Val	Pro	Pro	Arg	Leu	Ser	Lys	Glu	Glu	Leu	Ile	Gln	Asn	Met	
				165					170						175	
gac	cgc	gtg	gac	cga	gag	atc	acc	atg	gta	gag	cag	cag	atc	tct	aag	577
Asp	Arg	Val	Asp	Arg	Glu	Ile	Thr	Met	Val	Glu	Gln	Gln	Ile	Ser	Lys	
			180						185						190	
ctg	aag	aag	aag	cag	caa	cag	ctg	gag	gag	gag	gct	gcc	aag	ccg	ccc	625
Leu	Lys	Lys	Lys	Gln	Gln	Gln	Leu	Glu	Glu	Glu	Ala	Ala	Lys	Pro	Pro	
			195						200						205	
gag	cct	gag	aag	ccc	gtg	tca	ccg	ccg	ccc	atc	gag	tcg	aag	cac	cgc	673
Glu	Pro	Glu	Lys	Pro	Val	Ser	Pro	Pro	Pro	Ile	Glu	Ser	Lys	His	Arg	
	210								215						220	
agc	ctg	gtg	cag	atc	atc	tac	gac	gag	aac	cgg	aag	aag	gct	gaa	gct	721
Ser	Leu	Val	Gln	Ile	Ile	Tyr	Asp	Glu	Asn	Arg	Lys	Lys	Ala	Glu	Ala	
225					230					235					240	
gca	cat	cgg	att	ctg	gaa	ggc	ctg	ggg	ccc	cag	gtg	gag	ctg	ccg	ctg	769
Ala	His	Arg	Ile	Leu	Glu	Gly	Leu	Gly	Pro	Gln	Val	Glu	Leu	Pro	Leu	
			245						250						255	
tac	aac	cag	ccc	tcc	gac	acc	cgg	cag	tat	cat	gag	aac	atc	aaa	ata	817
Tyr	Asn	Gln	Pro	Ser	Asp	Thr	Arg	Gln	Tyr	His	Glu	Asn	Ile	Lys	Ile	
			260						265						270	
aac	cag	gcg	atg	cgg	aag	aag										



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Asn Gln Ala Met Arg Lys Lys Leu Ile Leu Tyr Phe Lys Arg Arg Asn	
275 280 285	
cac gct cgg aaa caa tgg aag cag aag ttc tgc cag cgc tat gac cag	913
His Ala Arg Lys Gln Trp Lys Gln Lys Phe Cys Gln Arg Tyr Asp Gln	
290 295 300	
ctc atg gag gcc ttg gaa aaa aag gtg gag cgc atc gaa aac aac ccg	961
Leu Met Glu Ala Leu Glu Lys Lys Val Glu Arg Ile Glu Asn Asn Pro	
305 310 315 320	
cgc cgg cgg gcc aag gag agc aag gtg cgc gag tac tac gaa aag cag	1009
Arg Arg Arg Ala Lys Glu Ser Lys Val Arg Glu Tyr Tyr Glu Lys Gln	
325 330 335	
ttc cct gag atc cgc aag cag cgc gag ctg cag gag cgc atg cag agc	1057
Phe Pro Glu Ile Arg Lys Gln Arg Glu Leu Gln Glu Arg Met Gln Ser	
340 345 350	
agg gtg ggc cag cgg ggc agt ggg ctg tcc atg tcg gcc gcc cgc agc	1105
Arg Val Gly Gln Arg Gly Ser Gly Leu Ser Met Ser Ala Ala Arg Ser	
355 360 365	
gag cac gag gtg tca gag atc atc gat ggc ctc tca gag cag gag aac	1153
Glu His Glu Val Ser Glu Ile Ile Asp Gly Leu Ser Glu Gln Glu Asn	
370 375 380	
ctg gag aag cag atg cgc cag ctg gcc gtg atc ccg ccc atg ctg tac	1201
Leu Glu Lys Gln Met Arg Gln Leu Ala Val Ile Pro Pro Met Leu Tyr	
385 390 395 400	
gac gct gac cag cag cgc atc aag ttc atc aac atg aac ggg ctt atg	1249
Asp Ala Asp Gln Gln Arg Ile Lys Phe Ile Asn Met Asn Gly Leu Met	
405 410 415	
gcc gac ccc atg aag gtg tac aaa gac cgc cag gtc atg aac atg tgg	1297
Ala Asp Pro Met Lys Val Tyr Lys Asp Arg Gln Val Met Asn Met Trp	
420 425 430	
agt gag cag gag aag gag acc ttc cgg gag aag ttc atg cag cat ccc	1345
Ser Glu Gln Glu Lys Glu Thr Phe Arg Glu Lys Phe Met Gln His Pro	
435 440 445	
aag aac ttt ggc ctg atc gca tca ttc ctg gag agg aag aca gtg gct	1393
Lys Asn Phe Gly Leu Ile Ala Ser Phe Leu Glu Arg Lys Thr Val Ala	
450 455 460	
gag tgc gtc ctc tat tac tac ctg act aag aag aat gag aac tat aag	1441
Glu Cys Val Leu Tyr Tyr Tyr Leu Thr Lys Lys Asn Glu Asn Tyr Lys	
465 470 475 480	
agc ctg gtg aga cgg agc tat cgg cgc cgc ggc aag agc cag cag caa	1489

Ser	Leu	Val	Arg	Arg	Ser	Tyr	Arg	Arg	Arg	Gly	Lys	Ser	Gln	Gln	Gln						
				485							490							495			
caa	cag	cag	cag	cag	cag	cag	cag	cag	cag	cag	cag	cag	cag	cag	ccc	atg	1537				
Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Pro	Met					
				500							505							510			
ccc	cgc	agc	agc	cag	gag	gag	aaa	gat	gag	aag	gag	aag	gaa	aag	gag		1585				
Pro	Arg	Ser	Ser	Gln	Glu	Glu	Lys	Asp	Glu	Lys	Glu	Lys	Glu	Lys	Glu						
				515							520							525			
gcg	gag	aag	gag	gag	gag	aag	ccg	gag	gtg	gag	aac	gac	aag	gaa	gac		1633				
Ala	Glu	Lys	Glu	Glu	Glu	Lys	Pro	Glu	Val	Glu	Asn	Asp	Lys	Glu	Asp						
				530							535							540			
ctc	ctc	aag	gag	aag	aca	gac	gac	acc	tca	ggg	gag	gac	aac	gac	gag		1681				
Leu	Leu	Lys	Glu	Lys	Thr	Asp	Asp	Thr	Ser	Gly	Glu	Asp	Asn	Asp	Glu						
				545							550							555			
aag	gag	gct	gtg	gcc	tcc	aaa	ggc	cgc	aaa	act	gcc	aac	agc	cag	gga		1729				
Lys	Glu	Ala	Val	Ala	Ser	Lys	Gly	Arg	Lys	Thr	Ala	Asn	Ser	Gln	Gly						
				565							570							575			
aga	cgc	aaa	ggc	cgc	atc	acc	cgc	tca	atg	gct	aat	gag	gcc	aac	agc		1777				
Arg	Arg	Lys	Gly	Arg	Ile	Thr	Arg	Ser	Met	Ala	Asn	Glu	Ala	Asn	Ser						
				580							585							590			
gag	gag	gcc	atc	acc	ccc	cag	cag	agc	gcc	gag	ctg	gcc	tcc	atg	gag		1825				
Glu	Glu	Ala	Ile	Thr	Pro	Gln	Gln	Ser	Ala	Glu	Leu	Ala	Ser	Met	Glu						
				595							600							605			
ctg	aat	gag	agt	tct	cgc	tgg	aca	gaa	gaa	gaa	atg	gaa	aca	gcc	aag		1873				
Leu	Asn	Glu	Ser	Ser	Arg	Trp	Thr	Glu	Glu	Glu	Met	Glu	Thr	Ala	Lys						
				610							615							620			
aaa	ggt	ctc	ctg	gaa	cac	ggc	cgc	aac	tgg	tcg	gcc	atc	gcc	cgg	atg		1921				
Lys	Gly	Leu	Leu	Glu	His	Gly	Arg	Asn	Trp	Ser	Ala	Ile	Ala	Arg	Met						
				625							630							635			
gtg	ggc	tcc	aag	act	gtg	tcg	cag	tgt	aag	aac	ttc	tac	ttc	aac	tac		1969				
Val	Gly	Ser	Lys	Thr	Val	Ser	Gln	Cys	Lys	Asn	Phe	Tyr	Phe	Asn	Tyr						
				645							650							655			
aag	aag	agg	cag	aac	ctc	gat	gag	atc	ttg	cag	cag	cac	aag	ctg	aag		2017				
Lys	Lys	Arg	Gln	Asn	Leu	Asp	Glu	Ile	Leu	Gln	Gln	His	Lys	Leu	Lys						
				660							665							670			
atg	gag	aag	gag	agg	aac	gcg	cgg	agg	aag	aag	aag	aaa	gcg	ccg	gcg		2065				
Met	Glu	Lys	Glu	Arg	Asn	Ala	Arg	Arg	Lys	Lys	Lys	Lys	Ala	Pro	Ala						
				675							680							685			
gcg	gcc	agc	gag	gag	gct	gca	ttc	ccg	ccc	gtg	gtg	gag	gat	gag	gag		2113				

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Ala Ala Ser Glu Glu Ala Ala Phe Pro Pro Val Val Glu Asp Glu Glu	
690 695 700	
atg gag gcg tcg ggc gtg agc gga aat gag gag gag atg gtg gag gag	2161
Met Glu Ala Ser Gly Val Ser Gly Asn Glu Glu Glu Met Val Glu Glu	
705 710 715 720	
gct gaa gcc tta cat gcc tct ggg aat gag gtg ccc aga ggg gaa tgc	2209
Ala Glu Ala Leu His Ala Ser Gly Asn Glu Val Pro Arg Gly Glu Cys	
725 730 735	
agt ggc cca gcc act gtc aac aac agc tca gac acc gag agc atc ccc	2257
Ser Gly Pro Ala Thr Val Asn Asn Ser Ser Asp Thr Glu Ser Ile Pro	
740 745 750	
tct cct cac act gag gcc gcc aag gac aca ggg cag aat ggg ccc aag	2305
Ser Pro His Thr Glu Ala Ala Lys Asp Thr Gly Gln Asn Gly Pro Lys	
755 760 765	
ccc cca gcc acc ctg ggc gcc gac ggg cca ccc cca ggc cca ccc acc	2353
Pro Pro Ala Thr Leu Gly Ala Asp Gly Pro Pro Pro Gly Pro Pro Thr	
770 775 780	
cca cca cgg agg aca tcc cgg gcc ccc att gag ccc acc ccg gcc tct	2401
Pro Pro Arg Arg Thr Ser Arg Ala Pro Ile Glu Pro Thr Pro Ala Ser	
785 790 795 800	
gaa gcc acc gga gcc cct acg ccc cca cca gca ccc cca tcg ccc tct	2449
Glu Ala Thr Gly Ala Pro Thr Pro Pro Pro Ala Pro Pro Ser Pro Ser	
805 810 815	
gca cct cct cct gtg gtc ccc aag gag gag aag gag gag gag acc gca	2497
Ala Pro Pro Pro Val Val Pro Lys Glu Glu Lys Glu Glu Glu Thr Ala	
820 825 830	
gca gcg ccc cca gtg gag gag ggg gag gag cag aag ccc ccc gcg gct	2545
Ala Ala Pro Pro Val Glu Glu Gly Glu Glu Gln Lys Pro Pro Ala Ala	
835 840 845	
gag gag ctg gca gtg gac aca ggg aag gcc gag gag ccc gtc aag agc	2593
Glu Glu Leu Ala Val Asp Thr Gly Lys Ala Glu Glu Pro Val Lys Ser	
850 855 860	
gag tgc acg gag gaa gcc gag gag ggg ccg gcc aag ggc aag gac gcg	2641
Glu Cys Thr Glu Glu Ala Glu Glu Gly Pro Ala Lys Gly Lys Asp Ala	
865 870 875 880	
gag gcc gct gag gcc acg gcc gag ggg gcg ctc aag gca gag aag aag	2689
Glu Ala Ala Glu Ala Thr Ala Glu Gly Ala Leu Lys Ala Glu Lys Lys	
885 890 895	
gag ggc ggg agc ggc agg gcc acc act gcc aag agc tcg ggc gcc ccc	2737

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Glu Gly Gly Ser Gly Arg Ala Thr Thr Ala Lys Ser Ser Gly Ala Pro	
900	905 910
cag gac agc gac tcc agt gct acc tgc agt gca gac gag gtg gat gag	2785
Gln Asp Ser Asp Ser Ser Ala Thr Cys Ser Ala Asp Glu Val Asp Glu	
915	920 925
gcc gag ggc ggc gac aag aac cgg ctg ctg tcc cca agg ccc agc ctc	2833
Ala Glu Gly Gly Asp Lys Asn Arg Leu Leu Ser Pro Arg Pro Ser Leu	
930	935 940
ctc acc ccg act ggc gac ccc cgg gcc aat gcc tca ccc cag aag cca	2881
Leu Thr Pro Thr Gly Asp Pro Arg Ala Asn Ala Ser Pro Gln Lys Pro	
945	950 955 960
ctg gac ctg aag cag ctg aag cag cga gcg gct gcc atc ccc ccc atc	2929
Leu Asp Leu Lys Gln Leu Lys Gln Arg Ala Ala Ala Ile Pro Pro Ile	
965	970 975
cag gtc acc aaa gtc cat gag ccc ccc cgg gag gac gca gct ccc acc	2977
Gln Val Thr Lys Val His Glu Pro Pro Arg Glu Asp Ala Ala Pro Thr	
980	985 990
aag cca gct ccc cca gcc cca ccg cca ccg caa aac ctg cag ccg gag	3025
Lys Pro Ala Pro Pro Ala Pro Pro Pro Pro Gln Asn Leu Gln Pro Glu	
995	1000 1005
agc gac gcc cct cag cag cct ggc agc agc ccc cgg ggc aag agc agg-	3073
Ser Asp Ala Pro Gln Gln Pro Gly Ser Ser Pro Arg Gly Lys Ser Arg	
1010	1015 1020
agc ccg gca ccc ccc gcc gac aag gag gcc ttc gca gcc gag gcc cag	3121
Ser Pro Ala Pro Pro Ala Asp Lys Glu Ala Phe Ala Ala Glu Ala Gln	
1025	1030 1035 1040
aag ctg cct ggg gac ccc cct tgc tgg act tcc ggc ctg ccc ttc ccc	3169
Lys Leu Pro Gly Asp Pro Pro Cys Trp Thr Ser Gly Leu Pro Phe Pro	
1045	1050 1055
gtg ccc ccc cgt gag gtg atc aag gcc tcc ccg cat gcc ccg gac ccc	3217
Val Pro Pro Arg Glu Val Ile Lys Ala Ser Pro His Ala Pro Asp Pro	
1060	1065 1070
tca gcc ttc tcc tac gct cca cct ggt cac cca ctg ccc ctg ggc ctc	3265
Ser Ala Phe Ser Tyr Ala Pro Pro Gly His Pro Leu Pro Leu Gly Leu	
1075	1080 1085
cat gac act gcc cgg ccc gtc ctg ccg cgc cca ccc acc atc tcc aac	3313
His Asp Thr Ala Arg Pro Val Leu Pro Arg Pro Pro Thr Ile Ser Asn	
1090	1095 1100
ccg cct ccc ctc atc tcc tct gcc aag cac ccc agc gtc ctc gag agg	3361

Pro Pro Pro Leu Ile Ser Ser Ala Lys His Pro Ser Val Leu Glu Arg	
1105	1110 1115 1120
caa ata ggt gcc atc tcc caa gga atg tcg gtc cag ctc cac gtc ccg	3409
Gln Ile Gly Ala Ile Ser Gln Gly Met Ser Val Gln Leu His Val Pro	
1125 1130 1135	
tac tca gag cat gcc aag gcc ccg gtg ggc cct gtc acc atg ggg ctg	3457
Tyr Ser Glu His Ala Lys Ala Pro Val Gly Pro Val Thr Met Gly Leu	
1140 1145 1150	
ccc ctg ccc atg gac ccc aaa aag ctg gca ccc ttc agc gga gtg aag	3505
Pro Leu Pro Met Asp Pro Lys Lys Leu Ala Pro Phe Ser Gly Val Lys	
1155 1160 1165	
cag gag cag ctg tcc cca cgg ggc cag gct ggg cca ccg gag agc ctg	3553
Gln Glu Gln Leu Ser Pro Arg Gly Gln Ala Gly Pro Pro Glu Ser Leu	
1170 1175 1180	
ggg gtg ccc aca gcc cag gag gcg tcc gtg ctg aga ggg aca gct ctg	3601
Gly Val Pro Thr Ala Gln Glu Ala Ser Val Leu Arg Gly Thr Ala Leu	
1185 1190 1195 1200	
ggc tca gtt ccg ggc gga agc atc acc aaa ggc att ccc agc aca cgg	3649
Gly Ser Val Pro Gly Gly Ser Ile Thr Lys Gly Ile Pro Ser Thr Arg	
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gtg ccc tcg gac agc gcc atc aca tac cgc ggc tcc atc acc cac ggc	3697
Val Pro Ser Asp Ser Ala Ile Thr Tyr Arg Gly Ser Ile Thr His Gly	
1220 1225 1230	
acg cca gct gac gtc ctg tac aag ggc acc atc acc agg atc atc ggc	3745
Thr Pro Ala Asp Val Leu Tyr Lys Gly Thr Ile Thr Arg Ile Ile Gly	
1235 1240 1245	
gag gac agc ccg agt cgc ttg gac cgc ggc cgg gag gac agc ctg ccc	3793
Glu Asp Ser Pro Ser Arg Leu Asp Arg Gly Arg Glu Asp Ser Leu Pro	
1250 1255 1260	
aag ggc cac gtc atc tac gaa ggc aag aag ggc cac gtc ttg tcc tat	3841
Lys Gly His Val Ile Tyr Glu Gly Lys Lys Gly His Val Leu Ser Tyr	
1265 1270 1275 1280	
gag ggt ggc atg tct gtg acc cag tgc tcc aag gag gac ggc aga agc	3889
Glu Gly Gly Met Ser Val Thr Gln Cys Ser Lys Glu Asp Gly Arg Ser	
1285 1290 1295	
agc tca gga ccc ccc cat gag acg gcc gcc ccc aag cgc acc tat gac	3937
Ser Ser Gly Pro Pro His Glu Thr Ala Ala Pro Lys Arg Thr Tyr Asp	
1300 1305 1310	
atg atg gag ggc cgc gtg ggc aga gcc atc tcc tca gcc agc atc gaa	3985

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PATENT

Met Met Glu Gly Arg Val Gly Arg Ala Ile Ser Ser Ala Ser Ile Glu	
1315 1320 1325	
ggt ctc atg ggc cgt gcc atc ccg ccg gag cga cac agc ccc cac cac	4033
Gly Leu Met Gly Arg Ala Ile Pro Pro Glu Arg His Ser Pro His His	
1330 1335 1340	
ctc aaa gag cag cac cac atc cgc ggg tcc atc aca caa ggg atc cct	4081
Leu Lys Glu Gln His His Ile Arg Gly Ser Ile Thr Gln Gly Ile Pro	
1345 1350 1355 1360	
cgg tcc tac gtg gag gca cag gag gac tac ctg cgt cgg gag gcc aag	4129
Arg Ser Tyr Val Glu Ala Gln Glu Asp Tyr Leu Arg Arg Glu Ala Lys	
1365 1370 1375	
ctc cta aag cgg gag ggc acg cct ccg ccc cca ccg ccc tca cgg gac	4177
Leu Leu Lys Arg Glu Gly Thr Pro Pro Pro Pro Pro Pro Ser Arg Asp	
1380 1385 1390	
ctg acc gag gcc tac aag acg cag gcc ctg ggc ccc ctg aag ctg aag	4225
Leu Thr Glu Ala Tyr Lys Thr Gln Ala Leu Gly Pro Leu Lys Leu Lys	
1395 1400 1405	
ccg gcc cat gag ggc ctg gtg gcc acg gtg aag gag gcg ggc cgc tcc	4273
Pro Ala His Glu Gly Leu Val Ala Thr Val Lys Glu Ala Gly Arg Ser	
1410 1415 1420	
atc cat gag atc ccg cgc gag gag ctg cgg cac acg ccc gag ctg ccc	4321
Ile His Glu Ile Pro Arg Glu Glu Leu Arg His Thr Pro Glu Leu Pro	
1425 1430 1435 1440	
ctg gcc ccg cgg ccg ctc aag gag ggc tcc atc acg cag ggc acc ccg	4369
Leu Ala Pro Arg Pro Leu Lys Glu Gly Ser Ile Thr Gln Gly Thr Pro	
1445 1450 1455	
ctc aag tac gac acc ggc gcg tcc acc act ggc tcc aaa aag cac gac	4417
Leu Lys Tyr Asp Thr Gly Ala Ser Thr Thr Gly Ser Lys Lys His Asp	
1460 1465 1470	
gta cgc tcc ctc atc ggc agc ccc ggc cgg acg ttc cca ccc gtg cac	4465
Val Arg Ser Leu Ile Gly Ser Pro Gly Arg Thr Phe Pro Pro Val His	
1475 1480 1485	
ccg ctg gat gtg atg gcc gac gcc cgg gca ctg gaa cgt gcc tgc tac	4513
Pro Leu Asp Val Met Ala Asp Ala Arg Ala Leu Glu Arg Ala Cys Tyr	
1490 1495 1500	
gag gag agc ctg aag agc cgg cca ggg acc gcc agc agc tcg ggg ggc	4561
Glu Glu Ser Leu Lys Ser Arg Pro Gly Thr Ala Ser Ser Ser Gly Gly	
1505 1510 1515 1520	
tcc att gcg cgc ggc gcc ccg gtc att gtg cct gag ctg ggt aag ccg	4609

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PATENT

Ser Ile Ala Arg Gly Ala Pro Val Ile Val Pro Glu Leu Gly Lys Pro	
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cgg cag agc ccc ctg acc tat gag gac cac ggg gca ccc ttt gcc ggc	4657
Arg Gln Ser Pro Leu Thr Tyr Glu Asp His Gly Ala Pro Phe Ala Gly	
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cac ctc cca cga ggt tgc ccc gtg acc atg cgg gag ccc acg ccg cgc	4705
His Leu Pro Arg Gly Ser Pro Val Thr Met Arg Glu Pro Thr Pro Arg	
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ctg cag gag ggc agc ctt tgc tcc agc aag gca tcc cag gac cga aag	4753
Leu Gln Glu Gly Ser Leu Ser Ser Ser Lys Ala Ser Gln Asp Arg Lys	
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ctg acg tgc acg cct cgt gag atc gcc aag tcc ccg cac agc acc gtg	4801
Leu Thr Ser Thr Pro Arg Glu Ile Ala Lys Ser Pro His Ser Thr Val	
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ccc gag cac cac cca cac ccc atc tgc ccc tat gag cac ctg ctt cgg	4849
Pro Glu His His Pro His Pro Ile Ser Pro Tyr Glu His Leu Leu Arg	
1605	1610 1615
ggc gtg agt ggc gtg gac ctg tat cgc agc cac atc ccc ctg gcc ttc	4897
Gly Val Ser Gly Val Asp Leu Tyr Arg Ser His Ile Pro Leu Ala Phe	
1620	1625 1630
gac ccc acc tcc ata ccc cgc ggc atc cct ctg gac gca gcc gct gcc	4945
Asp Pro Thr Ser Ile Pro Arg Gly Ile Pro Leu Asp Ala Ala Ala Ala	
1635	1640 1645
tac tac ctg ccc cga cac ctg gcc ccc aac ccc acc tac ccg cac ctg	4993
Tyr Tyr Leu Pro Arg His Leu Ala Pro Asn Pro Thr Tyr Pro His Leu	
1650	1655 1660
tac cca ccc tac ctc atc cgc ggc tac ccc gac acg gcg gcg ctg gag	5041
Tyr Pro Pro Tyr Leu Ile Arg Gly Tyr Pro Asp Thr Ala Ala Leu Glu	
1665	1670 1675 1680
aac cgg cag acc atc atc aat gac tac atc acc tgc cag cag atg cac	5089
Asn Arg Gln Thr Ile Ile Asn Asp Tyr Ile Thr Ser Gln Gln Met His	
1685	1690 1695
cac aac acg gcc acc gcc atg gcc cag cga gct gat atg ctg agg ggc	5137
His Asn Thr Ala Thr Ala Met Ala Gln Arg Ala Asp Met Leu Arg Gly	
1700	1705 1710
ctc tgc ccc cgc gag tcc tgc ctg gca ctc aac tac gct gcg ggt ccc	5185
Leu Ser Pro Arg Glu Ser Ser Leu Ala Leu Asn Tyr Ala Ala Gly Pro	
1715	1720 1725
cga ggc atc atc gac ctg tcc caa gtg cca cac ctg cct gtg ctc gtg	5233

Arg	Gly	Ile	Ile	Asp	Leu	Ser	Gln	Val	Pro	His	Leu	Pro	Val	Leu	Val	
1730				1735				1740								
ccc	ccg	aca	cca	ggc	acc	cca	gcc	acc	gcc	atg	gac	cgc	ctt	gcc	tac	5281
Pro	Pro	Thr	Pro	Gly	Thr	Pro	Ala	Thr	Ala	Met	Asp	Arg	Leu	Ala	Tyr	
1745				1750				1755				1760				
ctc	ccc	acc	gcg	ccc	cag	ccc	ttc	agc	agc	cgc	cac	agc	agc	tcc	cca	5329
Leu	Pro	Thr	Ala	Pro	Gln	Pro	Phe	Ser	Ser	Arg	His	Ser	Ser	Ser	Pro	
1765				1770				1775								
ctc	tcc	cca	gga	ggt	cca	aca	cac	ttg	aca	aaa	cca	acc	acc	acg	tcc	5377
Leu	Ser	Pro	Gly	Gly	Pro	Thr	His	Leu	Thr	Lys	Pro	Thr	Thr	Thr	Ser	
1780				1785				1790								
tcg	tcc	gag	cgg	gag	cga	gac	cgg	gat	cga	gag	cgg	gac	cgg	gat	cgg	5425
Ser	Ser	Glu	Arg	Glu	Arg	Asp	Arg	Asp	Arg	Glu	Arg	Asp	Arg	Asp	Arg	
1795				1800				1805								
gag	cgg	gaa	aag	tcc	atc	ctc	acg	tcc	acc	acg	acg	gtg	gag	cac	gca	5473
Glu	Arg	Glu	Lys	Ser	Ile	Leu	Thr	Ser	Thr	Thr	Thr	Val	Glu	His	Ala	
1810				1815				1820								
ccc	atc	tgg	aga	cct	ggt	aca	gag	cag	agc	agc	ggc	agc	agc	ggc	agc	5521
Pro	Ile	Trp	Arg	Pro	Gly	Thr	Glu	Gln	Ser	Ser	Gly	Ser	Ser	Gly	Ser	
1825				1830				1835				1840				
agc	ggc	ggg	ggt	ggg	ggc	agc	agc	agc	cgc	ccc	gcc	tcc	cac	tcc	cat	5569
Ser	Gly	Gly	Gly	Gly	Gly	Ser	Ser	Ser	Arg	Pro	Ala	Ser	His	Ser	His	
1845				1850				1855								
gcc	cac	cag	cac	tcg	ccc	atc	tcc	cct	cgg	acc	cag	gat	gcc	ctc	cag	5617
Ala	His	Gln	His	Ser	Pro	Ile	Ser	Pro	Arg	Thr	Gln	Asp	Ala	Leu	Gln	
1860				1865				1870								
cag	aga	ccc	agt	gtg	ctt	cac	aac	aca	ggc	atg	aag	ggt	atc	atc	acc	5665
Gln	Arg	Pro	Ser	Val	Leu	His	Asn	Thr	Gly	Met	Lys	Gly	Ile	Ile	Thr	
1875				1880				1885								
gct	gtg	gag	ccc	agc	aag	ccc	acg	gtc	ctg	agg	tcc	acc	tcc	acc	tcc	5713
Ala	Val	Glu	Pro	Ser	Lys	Pro	Thr	Val	Leu	Arg	Ser	Thr	Ser	Thr	Ser	
1890				1895				1900								
tca	ccc	gtt	cgc	cca	gct	gcc	aca	ttc	cca	cct	gcc	acc	cac	tgc	cca	5761
Ser	Pro	Val	Arg	Pro	Ala	Ala	Thr	Phe	Pro	Pro	Ala	Thr	His	Cys	Pro	
1905				1910				1915				1920				
ctg	ggc	ggc	acc	ctc	gat	ggg	gtc	tac	cct	acc	ctc	atg	gag	ccc	gtc	5809
Leu	Gly	Gly	Thr	Leu	Asp	Gly	Val	Tyr	Pro	Thr	Leu	Met	Glu	Pro	Val	
1925				1930				1935								
ttg	ctg	ccc	aag	gag	gcc	ccc	cgg	gtc	gcc	cgg	cca	gag	cgg	ccc	cga	5857



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PATENT

Leu Leu Pro Lys Glu Ala Pro Arg Val Ala Arg Pro Glu Arg Pro Arg	
1940	1945
1950	
gca gac acc ggc cat gcc ttc ctc gcc aag ccc cca gcc cgc tcc ggg	5905
Ala Asp Thr Gly His Ala Phe Leu Ala Lys Pro Pro Ala Arg Ser Gly	
1955	1960
1965	
ctg gag ccc gcc tcc tcc ccc agc aag ggc tcg gag ccc cgg ccc cta	5953
Leu Glu Pro Ala Ser Ser Pro Ser Lys Gly Ser Glu Pro Arg Pro Leu	
1970	1975
1980	
gtg cct cct gtc tct ggc cac gcc acc atc gcc cgc acc cct gcg aag	6001
Val Pro Pro Val Ser Gly His Ala Thr Ile Ala Arg Thr Pro Ala Lys	
1985	1990
1995	2000
aac ctc gca cct cac cac gcc agc ccg gac ccg ccg gcg cca cct gcc	6049
Asn Leu Ala Pro His His Ala Ser Pro Asp Pro Pro Ala Pro Pro Ala	
2005	2010
2015	
tcg gcc tcg gac ccg cac cgg gaa aag act caa agt aaa ccc ttt tcc	6097
Ser Ala Ser Asp Pro His Arg Glu Lys Thr Gln Ser Lys Pro Phe Ser	
2020	2025
2030	
atc cag gaa ctg gaa ctc cgt tct ctg ggt tac cac ggc agc agc tac	6145
Ile Gln Glu Leu Glu Leu Arg Ser Leu Gly Tyr His Gly Ser Ser Tyr	
2035	2040
2045	
agc ccc gaa ggg gtg gag ccc gtc agc cct gtg agc tca ccc agt ctg	6193
Ser Pro Glu Gly Val Glu Pro Val Ser Pro Val Ser Ser Pro Ser Leu	
2050	2055
2060	
acc cac gac aag ggg ctc ccc aag cac ctg gaa gag ctc gac aag agc	6241
Thr His Asp Lys Gly Leu Pro Lys His Leu Glu Glu Leu Asp Lys Ser	
2065	2070
2075	2080
cac ctg gag ggg gag ctg cgg ccc aag cag cca ggc ccc gtg aag ctt	6289
His Leu Glu Gly Glu Leu Arg Pro Lys Gln Pro Gly Pro Val Lys Leu	
2085	2090
2095	
ggc ggg gag gcc gcc cac ctc cca cac ctg cgg ccg ctg cct gag agc	6337
Gly Gly Glu Ala Ala His Leu Pro His Leu Arg Pro Leu Pro Glu Ser	
2100	2105
2110	
cag ccc tcg tcc agc ccg ctg ctc cag acc gcc cca ggg gtc aaa ggt	6385
Gln Pro Ser Ser Ser Pro Leu Leu Gln Thr Ala Pro Gly Val Lys Gly	
2115	2120
2125	
cac cag cgg gtg gtc acc ctg gcc cag cac atc agt gag gtc atc aca	6433
His Gln Arg Val Val Thr Leu Ala Gln His Ile Ser Glu Val Ile Thr	
2130	2135
2140	
cag gac tac acc cgg cac cac cca cag cag ctc agc gca ccc ctg ccc	6481

Gln	Asp	Tyr	Thr	Arg	His	Pro	Gln	Gln	Leu	Ser	Ala	Pro	Leu	Pro		
2145							2150			2155				2160		
gcc	ccc	ctc	tac	tcc	ttc	cct	ggg	gcc	agc	tgc	ccc	gtc	ctg	gac	ctc	6529
Ala	Pro	Leu	Tyr	Ser	Phe	Pro	Gly	Ala	Ser	Cys	Pro	Val	Leu	Asp	Leu	
							2165			2170				2175		
cgc	cgc	cca	ccc	agt	gac	ctc	tac	ctc	ccg	ccc	ccg	gac	cat	ggg	gcc	6577
Arg	Arg	Pro	Pro	Ser	Asp	Leu	Tyr	Leu	Pro	Pro	Pro	Asp	His	Gly	Ala	
							2180			2185				2190		
ccg	gcc	cgt	ggc	tcc	ccc	cac	agc	gaa	ggg	ggc	aag	agg	tct	cca	gag	6625
Pro	Ala	Arg	Gly	Ser	Pro	His	Ser	Glu	Gly	Gly	Lys	Arg	Ser	Pro	Glu	
							2195			2200				2205		
cca	aac	aag	acg	tcg	gtc	ttg	ggt	ggt	ggt	gag	gac	ggt	att	gaa	cct	6673
Pro	Asn	Lys	Thr	Ser	Val	Leu	Gly	Gly	Gly	Glu	Asp	Gly	Ile	Glu	Pro	
							2210			2220						
gtg	tcc	cca	ccg	gag	ggc	atg	acg	gag	cca	ggg	cac	tcc	cgg	agt	gct	6721
Val	Ser	Pro	Pro	Glu	Gly	Met	Thr	Glu	Pro	Gly	His	Ser	Arg	Ser	Ala	
2225							2230			2235					2240	
gtg	tac	ccg	ctg	ctg	tac	cgg	gat	ggg	gaa	cag	acg	gag	ccc	agc	agg	6769
Val	Tyr	Pro	Leu	Leu	Tyr	Arg	Asp	Gly	Glu	Gln	Thr	Glu	Pro	Ser	Arg	
							2245			2250				2255		
atg	ggc	tcc	aag	tct	cca	ggc	aac	acc	agc	cag	ccg	cca	gcc	ttc	ttc	6817
Met	Gly	Ser	Lys	Ser	Pro	Gly	Asn	Thr	Ser	Gln	Pro	Pro	Ala	Phe	Phe	
							2260			2265				2270		
agc	aag	ctg	acc	gag	agc	aac	tcc	gcc	atg	gtc	aag	tcc	aag	aag	caa	6865
Ser	Lys	Leu	Thr	Glu	Ser	Asn	Ser	Ala	Met	Val	Lys	Ser	Lys	Lys	Gln	
							2275			2280				2285		
gag	atc	aac	aag	aag	ctg	aac	acc	cac	aac	cgg	aat	gag	cct	gaa	tac	6913
Glu	Ile	Asn	Lys	Lys	Leu	Asn	Thr	His	Asn	Arg	Asn	Glu	Pro	Glu	Tyr	
							2290			2300						
aat	atc	agc	cag	cct	ggg	acg	gag	atc	ttc	aat	atg	ccc	gcc	atc	acc	6961
Asn	Ile	Ser	Gln	Pro	Gly	Thr	Glu	Ile	Phe	Asn	Met	Pro	Ala	Ile	Thr	
2305							2310			2315					2320	
gga	aca	ggc	ctt	atg	acc	tat	aga	agc	cag	gcg	gtg	cag	gaa	cat	gcc	7009
Gly	Thr	Gly	Leu	Met	Thr	Tyr	Arg	Ser	Gln	Ala	Val	Gln	Glu	His	Ala	
							2325			2330				2335		
agc	acc	aac	atg	ggg	ctg	gag	gcc	ata	att	aga	aag	gca	ctc	atg	ggg	7057
Ser	Thr	Asn	Met	Gly	Leu	Glu	Ala	Ile	Ile	Arg	Lys	Ala	Leu	Met	Gly	
							2340			2345				2350		
aaa	tat	gac	cag	tgg	gaa	gag	tcc	ccg	ccg	ctc	agc					

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PATENT

Lys Tyr Asp Gln Trp Glu Glu Ser Pro Pro Leu Ser Ala Asn Ala Phe  
2355 2360 2365  
aac cct ctg aat gcc agt gcc agc ctg ccc gct gct atg ccc ata acc 7153  
Asn Pro Leu Asn Ala Ser Ala Ser Leu Pro Ala Ala Met Pro Ile Thr  
2370 2375 2380  
gct gct gac gga cgg agt gac cac aca ctc acc tcg cca ggt ggc ggc 7201  
Ala Ala Asp Gly Arg Ser Asp His Thr Leu Thr Ser Pro Gly Gly Gly  
2385 2390 2395 2400  
ggg aag gcc aag gtc tct ggc aga ccc agc agc cga aaa gcc aag tcc 7249  
Gly Lys Ala Lys Val Ser Gly Arg Pro Ser Ser Arg Lys Ala Lys Ser  
2405 2410 2415  
ccg gcc ccg ggc ctg gca tct ggg gac cgg cca ccc tct gtc tcc tca 7297  
Pro Ala Pro Gly Leu Ala Ser Gly Asp Arg Pro Pro Ser Val Ser Ser  
2420 2425 2430  
gtg cac tcg gag gga gac tgc aac cgc cgg acg ccg ctc acc aac cgc 7345  
Val His Ser Glu Gly Asp Cys Asn Arg Arg Thr Pro Leu Thr Asn Arg  
2435 2440 2445  
gtg tgg gag gac agg ccc tcg tcc gca ggt tcc acg cca ttc ccc tac 7393  
Val Trp Glu Asp Arg Pro Ser Ser Ala Gly Ser Thr Pro Phe Pro Tyr  
2450 2455 2460  
aac ccc ctg atc atg cgg ctg cag gcg ggt gtc atg gct tcc cca ccc 7441  
Asn Pro Leu Ile Met Arg Leu Gln Ala Gly Val Met Ala Ser Pro Pro  
2465 2470 2475 2480  
cca ccg ggc ctc ccc gcg ggc agc ggg ccc ctc gct ggc ccc cac cac 7489  
Pro Pro Gly Leu Pro Ala Gly Ser Gly Pro Leu Ala Gly Pro His His  
2485 2490 2495  
gcc tgg gac gag gag ccc aag cca ctg ctc tgc tcg cag tac gag aca 7537  
Ala Trp Asp Glu Glu Pro Lys Pro Leu Leu Cys Ser Gln Tyr Glu Thr  
2500 2505 2510  
ctc tcc gac agc gag tga ctcagaacag ggcggggggg ggcgggagggt 7585  
Leu Ser Asp Ser Glu  
2515  
gtcagggtccc agcgagccac aggaacggcc ctgcaggagc ggggaggctg ccgactcccc 7645  
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Ala Ala Gly Pro Arg Gly Ile Ile Asp Leu Ser Gln Val Pro His Leu  
25 30 35  
cct gtg ctc gtg ccc ccg aca cca ggc acc cca gcc acc gcc atg gac 617  
Pro Val Leu Val Pro Pro Thr Pro Gly Thr Pro Ala Thr Ala Met Asp  
40 45 50  
cgc ctt gcc tac ctc ccc acc gcg ccc cag ccc ttc agc agc cgc cac 665  
Arg Leu Ala Tyr Leu Pro Thr Ala Pro Gln Pro Phe Ser Ser Arg His  
55 60 65 70

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PATENT

agc agc tcc cca ctc tcc cca gga ggt cca aca cac ttg aca aaa cca	713
Ser Ser Ser Pro Leu Ser Pro Gly Gly Pro Thr His Leu Thr Lys Pro	
75 80 85	
acc acc acg tcc tcg tcc gag cgg gag cga gac cgg gat cga gag cgg	761
Thr Thr Thr Ser Ser Ser Glu Arg Glu Arg Asp Arg Asp Arg Glu Arg	
90 95 100	
gac cgg gat cgg gag cgg gaa aag tcc atc ctc acg tcc acc acg acg	809
Asp Arg Asp Arg Glu Arg Glu Lys Ser Ile Leu Thr Ser Thr Thr Thr	
105 110 115	
gtg gag cac gca ccc atc tgg aga cct ggt aca gag cag agc agc ggc	857
Val Glu His Ala Pro Ile Trp Arg Pro Gly Thr Glu Gln Ser Ser Gly	
120 125 130	
agc agc ggc agc agc ggc ggg ggt ggg ggc agc agc agc cgc ccc gcc	905
Ser Ser Gly Ser Ser Gly Gly Gly Gly Gly Ser Ser Ser Arg Pro Ala	
135 140 145 150	
tcc cac tcc cat gcc cac cag cac tcg ccc atc tcc cct cgg acc cag	953
Ser His Ser His Ala His Gln His Ser Pro Ile Ser Pro Arg Thr Gln	
155 160 165	
gat gcc ctc cag cag aga ccc agt gtg ctt cac aac aca ggc atg aag	1001
Asp Ala Leu Gln Gln Arg Pro Ser Val Leu His Asn Thr Gly Met Lys	
170 175 180	
ggt atc atc acc gct gtg gag ccc agc acg ccc acg gtc ctg agg tcc	1049
Gly Ile Ile Thr Ala Val Glu Pro Ser Thr Pro Thr Val Leu Arg Ser	
185 190 195	
acc tcc acc tcc tca ccc gtt cgc cca gct gcc aca ttc cca cct gcc	1097
Thr Ser Thr Ser Ser Pro Val Arg Pro Ala Ala Thr Phe Pro Pro Ala	
200 205 210	
acc cac tgc cca ctg ggc ggc acc ctc gat ggg gtc tac cct acc ctc	1145
Thr His Cys Pro Leu Gly Gly Thr Leu Asp Gly Val Tyr Pro Thr Leu	
215 220 225 230	
atg gag ccc gtc ttg ctg ccc aag gag gcc ccc cgg gtc gcc cgg cca	1193
Met Glu Pro Val Leu Leu Pro Lys Glu Ala Pro Arg Val Ala Arg Pro	
235 240 245	
gag cgg ccc cga gca gac acc ggc cat gcc ttc ctc gcc aag ccc cca	1241
Glu Arg Pro Arg Ala Asp Thr Gly His Ala Phe Leu Ala Lys Pro Pro	
250 255 260	
gcc cgc tcc ggg ctg gag ccc gcc tcc tcc ccc agc aag ggc tcg gag	1289
Ala Arg Ser Gly Leu Glu Pro Ala Ser Ser Pro Ser Lys Gly Ser Glu	
265 270 275	

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PATENT

ccc cgg ccc cta gtg cct cct gtc tct ggc cac gcc acc atc gcc cgc 1337  
 Pro Arg Pro Leu Val Pro Pro Val Ser Gly His Ala Thr Ile Ala Arg  
 280 285 290  
 acc cct gcg aag aac ctc gca cct cac cac gcc agc ccg gac ccg ccg 1385  
 Thr Pro Ala Lys Asn Leu Ala Pro His His Ala Ser Pro Asp Pro Pro  
 295 300 305 310  
 gcg cca cct gcc tcg gcc tcg gac ccg cac cgg gaa aag act caa agt 1433  
 Ala Pro Pro Ala Ser Ala Ser Asp Pro His Arg Glu Lys Thr Gln Ser  
 315 320 325  
 aaa ccc ttt tcc atc cag gaa ctg gaa ctc cgt tct ctg ggt tac cac 1481  
 Lys Pro Phe Ser Ile Gln Glu Leu Glu Leu Arg Ser Leu Gly Tyr His  
 330 335 340  
 ggc agc agc tac agc ccc gaa ggg gtg gag ccc gtc agc cct gtg agc 1529  
 Gly Ser Ser Tyr Ser Pro Glu Gly Val Glu Pro Val Ser Pro Val Ser  
 345 350 355  
 tca ccc agt ctg acc cac gac aag ggg ctc ccc aag cac ctg gaa gag 1577  
 Ser Pro Ser Leu Thr His Asp Lys Gly Leu Pro Lys His Leu Glu Glu  
 360 365 370  
 ctc gac aag agc cac ctg gag ggg gag ctg cgg ccc aag cag cca ggc 1625  
 Leu Asp Lys Ser His Leu Glu Gly Glu Leu Arg Pro Lys Gln Pro Gly  
 375 380 385 390  
 ccc gtg aag ctt ggc ggg gag gcc gcc cac ctc cca cac ctg cgg ccg 1673  
 Pro Val Lys Leu Gly Gly Glu Ala Ala His Leu Pro His Leu Arg Pro  
 395 400 405  
 ctg cct gag agc cag ccc tcg tcc agc ccg ctg ctc cag acc gcc cca 1721  
 Leu Pro Glu Ser Gln Pro Ser Ser Ser Pro Leu Leu Gln Thr Ala Pro  
 410 415 420  
 ggg gtc aaa ggt cac cag cgg gtg gtc acc ctg gcc cag cac atc agt 1769  
 Gly Val Lys Gly His Gln Arg Val Val Thr Leu Ala Gln His Ile Ser  
 425 430 435  
 gag gtc atc aca cag gac tac acc cgg cac cac cca cag cag ctc agc 1817  
 Glu Val Ile Thr Gln Asp Tyr Thr Arg His His Pro Gln Gln Leu Ser  
 440 445 450  
 gca ccc ctg ccc gcc ccc ctc tac tcc ttc cct ggg gcc agc tgc ccc 1865  
 Ala Pro Leu Pro Ala Pro Leu Tyr Ser Phe Pro Gly Ala Ser Cys Pro  
 455 460 465 470  
 gtc ctg gac ctc cgc cgc cca ccc agt gac ctc tac ctc ccg ccc ccg 1913  
 Val Leu Asp Leu Arg Arg Pro Pro Ser Asp Leu Tyr Leu Pro Pro Pro  
 475 480 485

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PATENT

gac cat ggt gcc ccg gcc cgt ggc tcc ccc cac agc gaa ggg ggc aag	1961
Asp His Gly Ala Pro Ala Arg Gly Ser Pro His Ser Glu Gly Gly Lys	
490 495 500	
agg tct cca gag cca aac aag acg tcg gtc ttg ggt ggt gag gac	2009
Arg Ser Pro Glu Pro Asn Lys Thr Ser Val Leu Gly Gly Gly Glu Asp	
505 510 515	
ggt att gaa cct gtg tcc cca ccg gag ggc atg acg gag cca ggg cac	2057
Gly Ile Glu Pro Val Ser Pro Pro Glu Gly Met Thr Glu Pro Gly His	
520 525 530	
tcc cgg agt gct gtg tac ccg ctg ctg tac cgg gat ggg gaa cag acg	2105
Ser Arg Ser Ala Val Tyr Pro Leu Leu Tyr Arg Asp Gly Glu Gln Thr	
535 540 545 550	
gag ccc agc agg atg ggc tcc aag tct cca ggc aac acc agc cag ccg	2153
Glu Pro Ser Arg Met Gly Ser Lys Ser Pro Gly Asn Thr Ser Gln Pro	
555 560 565	
cca gcc ttc ttc agc aag ctg acc gag agc aac tcc gcc atg gtc aag	2201
Pro Ala Phe Phe Ser Lys Leu Thr Glu Ser Asn Ser Ala Met Val Lys	
570 575 580	
tcc aag aag caa gag atc aac aag aag ctg aac acc cac aac cgg aat	2249
Ser Lys Lys Gln Glu Ile Asn Lys Lys Leu Asn Thr His Asn Arg Asn	
585 590 595	
gag cct gaa tac aat atc agc cag cct ggg acg gag atc ttc aat atg	2297
Glu Pro Glu Tyr Asn Ile Ser Gln Pro Gly Thr Glu Ile Phe Asn Met	
600 605 610	
ccc gcc atc acc gga aca ggc ctt atg acc tat aga agc cag gcg gtg	2345
Pro Ala Ile Thr Gly Thr Gly Leu Met Thr Tyr Arg Ser Gln Ala Val	
615 620 625 630	
cag gaa cat gcc agc acc aac atg ggg ctg gag gcc ata att aga aag	2393
Gln Glu His Ala Ser Thr Asn Met Gly Leu Glu Ala Ile Ile Arg Lys	
635 640 645	
gca ctc atg ggt ggc ggc ggg aag gcc aag gtc tct ggc aga ccc agc	2441
Ala Leu Met Gly Gly Gly Gly Lys Ala Lys Val Ser Gly Arg Pro Ser	
650 655 660	
agc cga aaa gcc aag tcc ccg gcc ccg ggc ctg gca tct ggg gac cgg	2489
Ser Arg Lys Ala Lys Ser Pro Ala Pro Gly Leu Ala Ser Gly Asp Arg	
665 670 675	
cca ccc tct gtc tcc tca gtg cac tcg gag gga gac tgc aac cgc cgg	2537
Pro Pro Ser Val Ser Ser Val His Ser Glu Gly Asp Cys Asn Arg Arg	
680 685 690	

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PATENT

acg ccg ctc acc aac cgc gtg tgg gag gac agg ccc tcc gca ggt 2585  
 Thr Pro Leu Thr Asn Arg Val Trp Glu Asp Arg Pro Ser Ser Ala Gly  
 695 700 705 710  
 tcc acg cca ttc ccc tac aac ccc ctg atc atg cgg ctg cag gcg ggt 2633  
 Ser Thr Pro Phe Pro Tyr Asn Pro Leu Ile Met Arg Leu Gln Ala Gly  
 715 720 725  
 gtc atg gct tcc cca ccc cca ccg ggc ctc ccc gcg ggc agc ggg ccc 2681  
 Val Met Ala Ser Pro Pro Pro Pro Gly Leu Pro Ala Gly Ser Gly Pro  
 730 735 740  
 ctc gct ggc gcc cac cac gcc tgg gac gag gag ccc aag cca ctg ctc 2729  
 Leu Ala Gly Ala His His Ala Trp Asp Glu Glu Pro Lys Pro Leu Leu  
 745 750 755  
 tgc tcc cag tac gag aca ctc tcc gac agc gag tga ctcagaacag 2775  
 Cys Ser Gln Tyr Glu Thr Leu Ser Asp Ser Glu  
 760 765  
 ggcggggggg gcggggggcg gtgtcaggtc ccagcgagcc acaggaacgg ccctgcagga 2835  
 gcagggcggc tgccgactcc cccaaccaag gaaggagccc ctgagtcgc ctgcgcctcc 2895  
 atccatctgt ccgtccagag ccggcatcct tgcct 2930

&lt;210&gt; 14

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 14

agtcctcgtc atcagctcac

20

&lt;210&gt; 15

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;



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PATENT

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 15

20

ctcttggcag tggtaggcct

&lt;210&gt; 16

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 16

20

atgttcctgc accgcctggc

&lt;210&gt; 17

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 17

20

ctccagcgag gctgtgtcct

&lt;210&gt; 18

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

PTS-0012

-204-

PATENT

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 18

tcactggcac cagaaactgc

20

&lt;210&gt; 19

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 19

tggagcccga catggtggtg

20

&lt;210&gt; 20

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 20

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20

&lt;210&gt; 21

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

PTS-0012

-205-

PATENT

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 21

gctggccac cctctgcatg

20

&lt;210&gt; 22

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 22

gctggttgca gttttgcggc

20

&lt;210&gt; 23

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 23

ttgacagtgg cttcagcctc

20

&lt;210&gt; 24

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

PTS-0012

-206-

PATENT

<223> Antisense Oligonucleotide

<400> 24

aggcttctct gcctccttgt

20

<210> 25

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Antisense Oligonucleotide

<400> 25

tgtgctggga atgcctttgg

20

<210> 26

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Antisense Oligonucleotide

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20

<210> 27

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

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&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 27

gccgccacct ggcgaggtga

20

&lt;210&gt; 28

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 28

tggttctgagt cactcgctgt

20

&lt;210&gt; 29

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 29

catcatttac atctgccttt

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&lt;210&gt; 30

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

PTS-0012

-208-

PATENT

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20

<210> 31

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Antisense Oligonucleotide

<400> 31

gcatgtaagg cttcagcctc

20

<210> 32

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Antisense Oligonucleotide

<400> 32

ctcattccca gaggcattgta

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<210> 33

<211> 20

<212> DNA

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PTS-0012

-210-

PATENT

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<210> 37

<211> 20

<212> DNA

<213> Artificial Sequence

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<223> Antisense Oligonucleotide

<400> 37

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<210> 38

<211> 20

<212> DNA

<213> Artificial Sequence

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<223> Antisense Oligonucleotide

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<223> Antisense Oligonucleotide

<400> 40

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<210> 41

<211> 20

<212> DNA

<213> Artificial Sequence

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<210> 42

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<212> DNA

<213> Artificial Sequence

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PTS-0012

-212-

PATENT

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<210> 43

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<223> Antisense Oligonucleotide

<400> 43

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<210> 44

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Antisense Oligonucleotide

<400> 44

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20

<210> 45

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

PTS-0012

-213-

PATENT

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 45

ggcttctctg ctgagggcag

20

&lt;210&gt; 46

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 46

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&lt;210&gt; 47

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 47

cacttggtac ttactgccct

20

&lt;210&gt; 48

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

PTS-0012

-214-

PATENT

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 48

tcatatttac ccatgagtgc

20

&lt;210&gt; 49'

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 49

ggcctgcaga cctggcgagg

20

&lt;210&gt; 50

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Antisense Oligonucleotide

&lt;400&gt; 50

gccgccaccc atgagtgcct

20

&lt;210&gt; 51

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

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PATENT

&lt;400&gt; 51

agggccacca ctgccaagag

20

&lt;210&gt; 52

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 52

gccaggcggt gcaggaacat

20

&lt;210&gt; 53

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 53

aggacacagc ctcgctggag

20

&lt;210&gt; 54

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 54.

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&lt;210&gt; 55

&lt;211&gt; 20

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PATENT

<212> DNA

<213> H. sapiens

<220>

<400> 55

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20

<210> 56

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<212> DNA

<213> H. sapiens

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acaaggaggc agagaagcct

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<210> 57

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<220>

<400> 57

ccaaaggcat tcccagcaca

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<210> 58

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<212> DNA

<213> H. sapiens

<220>

<400> 58

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-217-

PATENT

ccgtcttgct gcccaaggag

20

&lt;210&gt; 59

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 59

tcacctcgcc aggtggcggc

20

&lt;210&gt; 60

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 60

acagcgagtg actcagaaca

20

&lt;210&gt; 61

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 61

catgcagagc aggggtgggccc

20

&lt;210&gt; 62

&lt;211&gt; 20

&lt;212&gt; DNA

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PATENT

<213> H. sapiens

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<400> 62

tacatgcctc tgggaatgag

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<210> 63

<211> 20

<212> DNA

<213> H. sapiens

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gacaaggagg ccttcgcagc

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<210> 64

<211> 20

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<213> H. sapiens

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<400> 64

taggaattca ggacactggg

20

<210> 65

<211> 20

<212> DNA

<213> H. sapiens

<220>

<400> 65

cccagcaggg tgggccagcg

20



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PATENT

&lt;210&gt; 66

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 66

ttccttccag ccttacatgc

20

&lt;210&gt; 67

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 67

agtggcccag gtacgaatgt

20

&lt;210&gt; 68

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

&lt;220&gt;

&lt;400&gt; 68

ctgccctcag cagagaagcc

20

&lt;210&gt; 69

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; H. sapiens

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PATENT

<220>

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ttcttcccag ccttcgcagc

20

<210> 70

<211> 20

<212> DNA

<213> H. sapiens

<220>

<400> 70

agggcagtaa gtaacaagtg

20

<210> 71

<211> 20

<212> DNA

<213> H. sapiens

<220>

<400> 71

gcactcatgg gtaaatatga

20

<210> 72

<211> 20

<212> DNA

<213> H. sapiens

<220>

<400> 72

cctcgccagg tctgcaggcc

20

